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ADDRESS OF THE PRESIDENT
HE SHALL HAVE A NOBLE MEMORY*

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Article II of the Constitution of the American Surgical Association reads as follows:

"The object of this Association shall be the cultivation and improvement of the science and art of surgery, the elevation of the medical profession and such other matters as may come legitimately within its sphere."

In his presidential address in 1937 Dr. Evarts Graham put into the mouth of our founder, Dr. Samuel Gross, certain words that have interested most of us ever since. He said "I also imagine that probably you have a standing committee working on the various problems concerned with the teaching of undergraduate surgery and with the later years of special training which you mentioned earlier. It is easy to see how this Association through a distribution of pamphlets on these subjects from time to time must hold the position of leadership in these important aspects of surgery which the founders dreamed for it." Well, there is no doubt that this Association has had much to say about graduate training in surgery and has taken a leading part in the wonderful transformation that has taken place in it. It is not so clear, however, that we have given the attention that our founder had in mind to the teaching of the undergraduate.

* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

In our meeting in Boston in 1935 you may remember that we had a symposium on the teaching of surgery in which Archibald, Cutler, Heuer and Whipple were the chief contributors and which was followed by a tremendous discussion by Bevan, Orr, Lewis, Pool, Rodman, Graham, McClure and myself.

This discussion was of great importance for it led to the extraordinary improvement in the quality of the training of surgeons and of surgical specialists that made itself so obvious during the War and is now showing its beneficent effect in civilian life.

The discussion of undergraduate teaching, however, was much less productive as there seemed to be a general feeling that conditions were pretty satisfactory in most of the medical schools. It was agreed that the urgent need at the time was an improvement in the graduate training of the surgeon with the establishment of higher standards. It was hoped that the day would come when the minimal standards set up would be required for licensure to practise.

But now that the programme for graduate training in surgery has been generally accepted it seems to me that we should go back again to the suggestion made by our founder and examine more carefully the teaching of the undergraduate. It is quite possible that the establishment of the training of the surgeon as a postgraduate study may have some effect on what the undergraduate should be taught.

As the years have rolled around tremendous changes have occurred in surgery which have caused equally tremendous changes in our curricula. When I was a student I had two bedside clinics and one didactic lecture a week extending over two clinical years of 30 weeks each. This covered the whole range of surgery exclusive of the eye, ear, nose and throat. Then gynaecology separated off and was awarded special clinical and didactic hours and almost immediately this same thing happened with urology. Then came orthopedic surgery, neurosurgery, and plastic surgery, each with its own specialists and each requiring a place in the curriculum. The result was the addition of a third clinical year. Now come thoracic surgery, vascular surgery, cancer surgery, and what not, all requiring special curricular arrangements. The result is that ten times as much space is given to the teaching of surgery as was given in 1903.

Now this is the phase of medical education that I wish to analyse. First of all, why do we teach all this surgery to medical students? Is it that conditions today are as they were 40 years ago and that every graduate must be taught enough surgery to enable him to carry out the less difficult operations that are indicated in general practice? Or is it that we have not made the changes in our curricula that our greatly changed policy in regard to surgery demands. This Association and all other national associations along with the American and Canadian colleges are committed to the principle that major surgery shall be done only by those who have been adequately

trained for it. For the young men and women who wish to do surgery today we are demanding five years of postgraduate supervised training plus the passing of stiff examinations. Then why teach the enormously increased amount of surgery of our present day curricula to thousands of medical students who are going to be physicians or public health officers or ordinary general practitioners? As far as the latter are concerned, I suggest that it is not only unnecessary but it is actually dangerous, for as long as our state and provincial licensing boards continue to grant the right to practise surgery to untrained men, as they do today, this half-baked undergraduate training is a temptation to less scrupulous practitioners to do what they ought not to do. It actually tends to perpetuate the evil which our program of graduate training is trying to end.

It is not for me to tell you how to overcome this anomalous situation whereby, as Elliott Cutler has said, the American public may legally be cared for, indeed subjected to a dangerous surgical procedure by a student who has just graduated from medical school. As far as my own country is concerned, however, I propose to devote much of the remainder of my life to an effort to provide enough properly trained surgeons to take care of our people and to preventing those who are not so trained from having a part in it.

The answer, of course, is that we should review our curricula in the light of the changes that have occurred in surgery and of the new policy we have adopted towards it. The time has now come when the study of surgery must be established as a postgraduate course with not only the apprenticeship in hospital but also a special curriculum of studies covering surgery itself and all the appropriate basic sciences. In the undergraduate years it should be reduced to what might be described as an introduction to surgery with special emphasis on applied anatomy, physiology and pathology, on methods of examination and on the diagnosis of those diseases and injuries that are ordinarily found in the Department of Surgery. I am suggesting, indeed, that the teaching of such subjects as peptic ulcer, carcinoma of the stomach, tumour of the brain, bronchiectasis and dozens of others should be either conducted by the physicians or if by us, then as physicians and not as surgeons. Our time will come when the young graduate is definitely committed to the program which we have agreed is necessary for the training of a modern surgeon.

Since I have been turning this subject over in my mind I have found a tremendous variation in the curricula of the schools scattered over the country. A survey made recently by the orthopedic surgeons showed a total lack of unanimity in regard to what should be taught and the same thing seems to be true of all the specialties and, indeed, of general surgery itself. In some schools each specialty is an entirely separate department which has no integration with the other departments except through the dean. The result is repetition, neglect of general fundamental principles and gross waste

of time. And even in schools where the surgical specialties are sub-departments of general surgery the tendency is to teach the specialty rather than the simple fundamentals. Indeed, it has been my observation that quite frequently the members of the various special departments are neither interested in nor capable of teaching the applied physiology, biochemistry, and pathology which must be mastered by the undergraduate in order that he may understand disease.

Along with the growth of surgery has come a corresponding increase in the size of the textbooks. As a Professor of Surgery I must have a dozen different textbooks entitled 'The Principles and Practice of Surgery' all sent by the publishers in the hope that they would be recommended for the students. The preface in each case states that the book was written especially 'for students and practitioners'. Now as far as the undergraduates are concerned the 14 or 15 hundred pages in these books are about three times too many and for the practitioners, that is the surgeons, they are not nearly enough. It seems to me that a textbook for undergraduate students should be limited to 'principles' and should contain only minimal reference to 'practice'. What the student needs is help, both from his instructors and from his textbooks, in the art of examining the patient and eliciting and interpreting physical signs; help, too, in understanding the underlying pathology and linking it up with the history, the symptons and signs, the probable diagnosis, the prognosis and the indications for treatment. The actual 'practice' is something for postgraduate study.

Now I am perfectly aware that the views I am expressing here are highly controversial and will probably be irritating to many of us who have school organizations that have received my criticism. To them I offer my humble apologies and present as an excuse my own feeling of uncertainty and my sincere desire for the help of all who think of these things, to arrive at a good solution. It is my hope that at some time during this meeting this Association will see fit to appoint a committee to make a survey of the whole subject of undergraduate teaching of surgery in America and elsewhere and to bring in a report on some future occasion which will give us a true picture of conditions as they are at present and as we would like to see them in the future.

It is my thought that this survey should cover the principal schools of America and Europe and that it should be based on visits to these institutions as well as on questionnaires. Such a survey would not be aimed at making comparisons of one school with another but would be directed solely towards finding out what is best in each in order that we may be in a position to do what Dr. Gross thought we should be doing in regard to the undergraduate teaching of surgery.

The second problem I wish to discuss is that of the full time professorships in surgery. It is just 20 years since I accepted such an appointment

and as I have been interested not only in my own difficulties but also in those of other full time professors I am in a position to make some comments.

First of all let me assure you that I have no regrets and that I would do it again without the slightest qualm. The organization of a school for surgeons was what I wanted to do more than anything else and it couldn't be done except on some sort of full time basis.

It should be appreciated, however, that it cannot be done without a great financial sacrifice. Unless the satisfaction that the professor gets out of his position and out of the opportunities which his position affords him is sufficient to outweigh the loss of private income he should not accept the appointment. There isn't the remotest possibility for a first-class professor to command an income either from his salary or from a limited amount of consultation practice, comparable to what he could expect from private work.

Again, when a professor accepts a full time or a modified full time appointment he should be assured of an adequate pension when he retires. I have no personal cause for complaint in this regard for although my pension is only a token yet this was compensated for by an arrangement whereby my retiring time would be at the age of 65 instead of the regulation 60. Whether retirement comes, however at 65 or 60 there should be an adequate pension for there isn't a chance in the world, no matter how distinguished and accomplished the professor may be, of picking up private practice again in competition with the young men he has trained. This business of dropping a professor of surgery at 60 or thereabouts without an adequate pension is sure to prevent us, in the long run, from getting the best men for the full time chairs.

The selection of the Professor of Surgery, next to that of the Professor of Medicine is the most important duty of the Dean. Having in mind that the most important duty of a professor is the training of surgeons, I would recommend to the Dean that he select as Professor of Surgery a first-class surgeon who can command the respect and admiration of his students. There is nothing sadder than to see a great chair occupied by a well meaning man who arouses in his colleagues and students a feeling of pity. If I were a young fellow again embarking on a surgical training I would pick out for my teacher one of the young professors in this society, particularly one with a stimulating personality, an enquiring turn of mind, and a background of training and performance that left no doubt that he was a good surgeon. Indeed, I expect that is what we all did.

The point, however, that this professor must be a first-class surgeon calls for comment. I note a tendency from time to time to appoint as professors men who are so young that they have never been heard of as surgeons. They may have had excellent training in hospital and laboratory, they may have done good research work and they may be good lecturers and clinicians but is there any certainty that they are really good surgeons? Would you

have them make the decision and carry out the treatment if you were desperately ill? It is considerations such as these that make me think that the new professors should not be selected from those who have recently completed their training but rather from those whose early maturity has confirmed the promise of the their youth.

I hope these remarks will not be considered reactionary for I am in hearty sympathy with the modern tendency to require in professors a broad training in physiology and biochemistry and an ability to use it in surgical research. All I am doing is making the selection of the professor more difficult by demanding that he be also a good surgeon.

The question of whether the professor shall be selected from the surgical specialists or from the so-called general surgeons, whom the specialists refer to as specialists in the small part of surgery that is left to them, namely the abdomen, thyroid and breast, is a difficult one. Many of the chairs of surgery in America have been and are occupied by most distinguished specialists. It is my impression, however, that unless such professors revert to the general surgery from which they came, they cannot give the leadership of the whole department that their position demands. They often act simply as chairmen of the department and exert their influence in an executive way rather than by leadership. While there is no harm in a professor knowing a great deal about some small part of surgery, it is equally essential that he know a great deal, or at any rate, a considerable amount about all branches of surgery.

This means, (if it is true) that the professor must be very specially trained. Not only must he have had adequate experience in anatomy, physiology and biochemistry, preferably with research experience in at least one of them, but he must have had a very broad training in surgery itself, including neurosurgery, orthopedic surgery, urology, thoracic surgery and so on, and he must be competent to discuss the general problems that arise in each. It begins to look, therefore, as if the candidates for the chairs will have to plan their training a long way back and with academic life definitely in mind in order that they may have the broad education that their position requires.

Looking over the field in America and Great Britain it seems to me that the places where the so-called full time professorships have worked best are those where the professor is also surgeon-in-chief of the hospital. Under such circumstances, if he is the ideal man for the appointment, the whole surgical service will have the benefit of his leadership and the school and the hospital will work as a unit. In those instances where the professorial unit comprises only one of several surgical services, and is on an equal basis and in competition with them, there is unhappiness and often bitterness. The professor and his full time staff, on salaries of a certain amount, look on their colleagues on the other services as rolling in wealth and the effect is demoralizing. The other services respond by belittling the professorial

service as composed of men who can face only a protected existence and could not compete in the open market. And so it goes. After looking them all over I wouldn't accept a chair of surgery unless it carried with it the post of a surgeon-in-chief of the main university hospital.

Looking back over the years of the full time professorships in America I would say that they have come to stay. You cannot run a first class school and particularly a first class postgraduate school for surgeons without them. To make the show go the professor must be on the job morning, noon, and night. He must teach and he must teach others to teach; he must operate and he must teach others to operate; and he must lead in research and act as a constant liaison with all the research departments. When you add to this the never ending rounds, staff meetings, committee meetings, and everything else it is easily seen that the day of the old time professor with the large private practice is over.

On the other hand the experiment of the full time professorship, in spite of the difficulties that have been encountered, has worked amazingly well. Under this system the departments of surgery have flourished; research, as evidenced in our program to-day, has taken on a new life; and schools for the training of surgeons have sprung up everywhere. Indeed the chief accomplishment of the full time professor up to the present has been the establishment of our modern system of graduate training for surgeons. The standards which have been set up by the Colleges of Surgery and the various Boards have been accepted by the schools and there is little doubt that the quality of the candidates for fellowship or for certification is being steadily improved.

The setting of high standards, however, brings with it the necessity for special instruction. It wasn't long after the establishment of the Royal College examinations in Canada that a demand arose for refresher courses and special instructional classes that would prepare the candidates for the examinations. At first these were conducted extramurally by private arrangement, but more recently the universities have recognized their responsibility and have established postgraduate curricula for the residents and assistant residents in training. These graduate students, in addition to their routine work in the hospital, now take regular courses in anatomy, physiology, biochemistry, pathology and surgery.

Placed as we Canadians are in close relationship both to the British and to the Americans, we are in an excellent position to observe the working of each system. I am of the opinion that the English students going up for their fellowship examinations are infinitely better prepared in the basic medical sciences than are ours. On the other hand they have had nothing like the practical supervised hospital training that our men have had. In our recent visit to England, however, we found that full time professorial chairs are being established all over the country and that plans are being laid for adequate graduate training comparable to

the system here. I wish I felt sure that we were as aware of the weak spot in our system, that is, in the basic sciences, as the English are of theirs.

You will recall the brilliant address of our president, Dr. David Cheever, when he drew attention to the fact that the teaching and the study of anatomy on this side of the Atlantic had fallen on evil days, was largely in the hands of Arts professors and from the standpoint of the surgeon had suffered a complete eclipse.

Well, what have we done about it? Serving as I have on the Committee on Graduate Training in the American College of Surgeons I have heard a lot of chatter about adequate training in the basic sciences, but I haven't heard much about our residents going back to the dissecting room to learn their anatomy properly. Until they do I am perfectly sure they will not be able to make a first class physical examination. The surgeon, when he looks at a limb, an abdomen, or a neck, should be able to see right through it.

The remedy, it seems to me, is twofold. First, we should require the candidates for fellowship or certification to pass a stiff examination in all the basic medical sciences as well as in surgery. Second, we should plan the four or five years of internship so that the students can receive such really first class instruction in these subjects that they can face the examination with equanimity.

When I began thinking over what I might say that would be of interest to the Association I fully made up my mind that a serious discussion of a scientific subject by an old fellow who is looking mostly on the past would be out of place. However, knowing as I do that the younger members come here to learn scientific surgery and not to discuss medical education I have decided to close my address in a lighter vein with some observations calculated to wake them up and perhaps to irritate them.

First of all I wish to suggest that surgeons as a class are grossly unscientific. When one remembers that our daily work involves the health and indeed the very lives of our patients is it not appalling that it takes us so long to learn the truth about anything? Take, for example, the surgical treatment of duodenal ulcer. Forty years ago the first gastroenterostomy was performed. Within a decade, through the influence of a few strong personalities it swept over the whole world and hundreds of thousands of patients were submitted to it. It took us twenty more years to find out that it was all nonsense. And why? The answer is, failure to study the effect of the operation on animals, failure to conduct adequate follow up studies on patients and failure to try to understand and to apply the simple rules of statistics. Let me suggest that each of us take the current issues of the best known surgical journals and see how many of the papers are based on anything but wishful thinking.

I bring the subject up in order to introduce my pet hobby of the use of foreign bodies in surgery. Please do not think that I am objecting seriously

to their use, for the largest part of my practice nowadays consists of taking them out. I simply want to draw your attention to our gross neglect of the scientific method.

A review of all the operations involving the introduction of foreign bodies would fill a book. Murphy's button, McGraw's ligature, vitallium bile duct tubes, have all given place to more physiological procedures designed to imitate as closely as possible the normal. Lane plates, vitallium plates, and now tantalum plates each have their proponents and each have their proportion of disastrous results. Stader splints, Roger Anderson pins, Smith-Petersen nails, icetongs, Steinman pins, Kirschner wires, Parham bands, and Kunscher nails have all given rise to special surgical techniques designed to undo the harm they have done. Some of them, such as the Steinman pin or Kirschner wire through the oscalcis can cause an osteomyelitis of the body of that bone that we haven't yet learned how to cure. Then there are the silver plates, gold plates, celluloid plates, acrylic plates and tantalum plates used in the repair of defects in the skull. Each has been strongly advocated in our surgical journals without a shred of scientific support, except that the patients seem to survive the operations. And besides all this we have the never ending squabble about sutures—silk threads, linen threads, cotton threads, and catgut, each surgeon thinking that the reason his results are so much better than he expected is because of his special material or of the way he uses it. And now we are in the midst of the steel wire era. This is particularly annoying to me because in dealing with the postoperative hernias which result from the use of these cutting sutures I invariably spoil the edges of my knives. The other day I saw a man with an infected finger which had resulted from a puncture by the end of one of these wires which had worked its way out of a recent hernia wound and got mixed up with the contents of his trousers pocket.

Seriously, however, the matter does call for some consideration. I am not one to condemn holus bolus the use of foreign bodies in surgery for I know full well that great advances have been made because of them. And often enough, as in the case of the Murphy button, the combination of the good and the harm that they did has led to a really successful solution of a difficulty. On the other hand, the complications, the failures, and the actual disasters that have attended their use have been so universal that there isn't any question we should pause before using them. If it is obvious that to do a great good we must do a little harm then we must go ahead and do it, but if the desired result can be obtained without the risk attending a little harm then we should by all means avoid it. It would seem particularly important that when the ingenious surgeon feels the urge to add some new foreign body to our armamentarium he should pause and see whether he cannot then and there figure out the physiological procedure by which his bright idea, if it really is a good one, will surely be replaced.

I said a moment ago that we are very unscientific. I had in mind the

abandon with which we try out new ideas on patients without studying the results on animals; and also our naivety in thinking that an experience of a few cases justifies final conclusions and the publication of results. Have you ever noticed how a street railway or a bus company will count the passengers at certain points, day after day, before making a change in the route; or how a hydraulic engineer will measure the rate of flow of a stream at every month in the year before developing his plans for harnessing it? But these are studies which involve nothing but the expenditure of money, whereas we are dealing with human lives. How much more important, therefore, that we should test our ideas thoroughly before trying them on our patients or committing them to print.

Membership in this Association is a wonderful thing. I remember the thrill of delight with which I read the telegrams of congratulation that came in one Saturday afternoon after my election. I recall, too, the wonderful stimulation I have received from my unbroken attendance at its meetings for the past 26 years. Nothing that could have happened to me could have helped me more on the rough road of a surgical career.

The recollection of these early years stirs me to repeat what several of my predecessors in this chair have said, namely, that in selecting our new members each year we should choose young men who have a large part of their productive career ahead of them and who give promise of being able to take part in our discussions in a constructive way; men who as a result of close association with the distinguished members of our Society may develop even more fully than they could otherwise have done. It seems to me that we should reserve the election of men who are close to or past the retiring age—to a very distinguished few—no matter how distinguished they may be.

Our membership, indeed, is divided according to age into three broad groups. First and most important are the young, upon whom we must depend for the advancement of our art and science. Then come the middle aged who represent success and who are in command of our educational programme. To them let me recall the demand of our people from the Atlantic to the Pacific and from Hudson's Bay to the Rio Grande for first class surgical care. To provide it we must turn out hundreds of well qualified men every year. This means that every medical school and every first class hospital must join together in providing our young graduates with the necessary years of supervised internship and residency and with well planned postgraduate courses in anatomy, physiology, biochemistry, and surgery. Unless we present our candidates properly trained our Board of Surgery and our Colleges of Surgeons, because of the standards they are setting, will defeat rather than help in providing for the surgical care of our people. I suggest that for the next 20 or 30 years the chief duty of the members of this Association is to give leadership and guidance in this great program of Graduate Training in Surgery.

And finally, there is among our membership a smaller group who once belonged to the other two but who, because of the lapse of time are now senior members. I note with sadness that there are only ten men here today who were present at my first meeting and that there are only 25 members left of the 200 who were members then. The loss this year of our beloved President, Elliott Cutler, of our distinguished Honorary Member, Sir John Fraser, the Principal of Edinburgh University, and of my close friends John McCreary, Roscoe Graham, and Fraser Gurd and William Darrach brings thoughts that are sad indeed. On behalf of those who are in the senior group, however, let me assure you that we shall be coming to these meetings as long as we can walk. We want to see and hear the new members, to mingle with the young men who we hope will carry the traditions of the Society to even greater glories than in the past, and to renew our delightful associations with old friends. That you from time to time honour one of us by electing him to be your President brings great happiness to us all.

STRICTURES OF THE COMMON DUCT*

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ALTHOUGH THERE HAS BEEN GREAT IMPROVEMENT in the results following repair of strictures of the common duct during recent years, the outcome is far from that desired. Since the results are by no means perfect, and since such a large percentage of strictures are caused by operative trauma, meticulous attention must be paid to the technic of operations on the biliary tract in the prevention of these lesions.

ETIOLOGY OF STRICTURES OF THE COMMON DUCT

In our series of 49 patients, operative trauma could be identified as the direct cause of the stricture in 65 per cent (Table I). In this group jaundice or a biliary fistula developed in one to three days following an operation on the biliary tract (usually cholecystectomy).

Numerous mechanisms in production of operative trauma are possible (Fig. 1). Perhaps the most common is excision of a mobile common duct which is placed under tension by traction on the gallbladder; the common duct is erroneously identified as part of the cystic and a portion excised. Another common mechanism is ligation of a portion or all of the duct with a bleeding vessel. It is possible that when considerable effort is made to ligate the cystic duct close to the common, the latter structure may be damaged. Occasionally, the duct is damaged during gastrectomy or traumatized sufficiently during choledochostomy to result in stricture formation; however, in our series none of the strictures could be attributed to either of these two causes.

In 11 patients, or 23 per cent of our series, an interval of three months to six years lapsed following the operation on the biliary tract before evidence of the stricture developed. The mechanism in production of these delayed strictures is poorly understood, but the authors agree with the original contention of Judd[1], that a gradual obliterative cholangitis does occur and appears to be related primarily to inflammation. There are several possible causes of this inflammatory process in the wall of the common duct. The authors believe that a collection of bile overlying the common duct is a common cause of delayed formation of a stricture. A small abscess might produce a stenosis in the same manner. On other occasions neither of these two mechanisms appear to exert a role in production of the stricture. We

* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

have had the same experience noted by Judd years ago, that a common duct observed at one operation was relatively normal in size, but at another operation several months later had stenosed down to a mere fibrous cord.

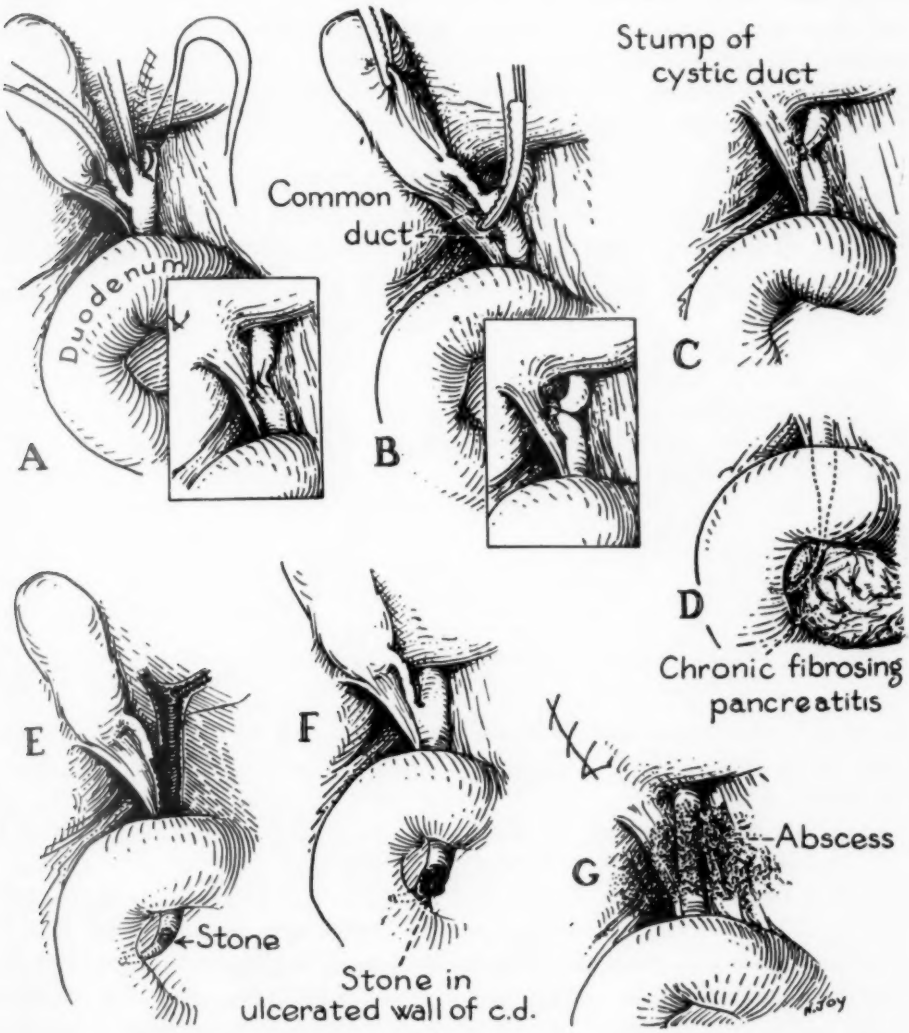

FIG. 1.—Mechanisms in production of stricture of the common duct; (A) transfixion with a needle; (B) ligation with the cystic duct; (C) ligation of the cystic duct too close to the common; (D) diffuse sclerosing pancreatitis; (E) chlolangitis; (F) ulceration of the wall by stone; (G) abscess or local collection of bile. (From Cole, Ireneus and Reynolds, in Strictures of the Common Duct, Interscience Publishing Co.. New York. In Press.)

Large masses of catgut and ligated tissue left adjacent to the common duct at the time of cholecystectomy might act as the source of an inflammatory process. On some occasions pylephlebitis appears to be the cause of the inflammatory stenosis. We have had four patients in our series of patients

with stricture who had pylephlebitis; it seems possible that this lesion may have been the primary etiologic factor in the production of stricture in these cases, primarily by contact infection.

In five patients, or 10 per cent of the series, the stricture was due to chronic pancreatitis of the diffuse fibrosing type. In two of these the obstruction was not complete.

Other factors such as pancreatic cysts, ulceration due to gall stones, etc., exist, but are relatively uncommon.

PREVENTION OF STRICTURES

Numerous measures can be utilized in operations on the biliary tract to prevent trauma to the common duct. If particular attention is paid to these

TABLE I.—*Causes of Benign Strictures of the Common Bile Duct (In Our Series of 49 Patients*)*

	No. of Cases	*Per Cent*
1. Operative trauma (none following choledochostomy or gastrectomy)	32	65
2. Inflammation (some possibly related to trauma)	11	23
3. Chronic pancreatitis	5	10
4. Pancreatic cyst	1	2
Total	49	100

* Only 4 patients (excluding the pancreatitis cases) were jaundiced before the original operation.

prophylactic measures the incidence of trauma will be diminished. Space does not permit detailed discussion of the measures, but they will be enumerated briefly below.

1. Maintain carefulness, and refrain from hurry while dissecting structures near the common duct.
2. Obtain good exposure of the region about the common duct with a long incision. The incision may be oblique, transverse or longitudinal, but should be of sufficient length to give adequate exposure.
3. Obtain adequate relaxation with the proper anesthetic. Ether is an adequate anesthetic in obtaining this relaxation, but cyclopropane and curare are likewise effective.
4. Isolate the junction of the common duct and the cystic duct before ligating the latter structure.
5. Ligate no artery until it is proven that it enters the gallbladder.
6. Ligate the cystic duct and artery separately.
7. Cut no structure until it is identified.
8. Ligate the cystic duct at least ½ inch from the common duct. This distance will protect the common duct and likewise prevent reformation of a bulbous tip.

9. Control hemorrhage by pressure with the index finger of the left hand in the foramen of Winslow against the thumb, so the bleeding point can be controlled by compressing the hepatic artery. By gradual release of compression the bleeding point can be identified and caught accurately with an artery forcep.
10. If adhesions are dense around the common duct, start dissection at the fundus of the gallbladder and ligate the duct or ampulla high.
11. Eradicate gallbladder disease early before massive inflammation takes place.
12. Be familiar with the abnormal anatomy as well as the "normal". The anatomy of the biliary tract is so varied that we can identify no position of the various structures as normal. Normal can only be considered a composite of those types most commonly observed.

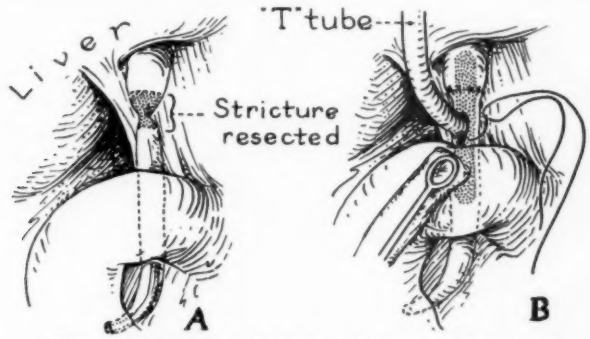

FIG. 2.—Repair of local stricture is best accomplished by resection of the stenosed area and end to end anastomosis. Support of the suture line is necessary for at least 3 months and is best accomplished by the arm of a T tube inserted through an opening ½ inch from the suture line. Every effort should be made to find the distal end of the common duct because the end to end type of repair, as illustrated above, is by far the most successful. (From Cole, Ireneus and Reynolds, in Strictures of the Common Duct, Interscience Publishing Co., New York. In press.)

REPAIR OF STRICTURES

Since numerous types of stricture are encountered, numerous operative procedures must be available for the repair. It is now agreed by most surgeons spending considerable thought on repair of strictures of the common duct that the most difficult type to repair from the standpoint of recurrence, is the one occurring at the hilus of the liver. Unfortunately, when a stricture reforms, it is frequently at this point. Therefore, it is the opinion of the authors that the greatest improvement to be obtained in the repair of strictures would be in that group occurring at the hilus. Space does not permit a detailed discussion of the repair of the various types of strictures. Therefore, most of the text dealing with repair of stricture will be devoted to the details of a procedure which the authors have devised for treatment of strictures at the hilus. Other common procedures will be discussed briefly.

1. Local Strictures.—When a stricture is localized to a small portion of the common duct and does not involve the hilus of the liver, repair is easily performed by excising the scar at the stricture and performing an end-to-end anastomosis. One layer of sutures is adequate for end-to-end repair. Non-absorbable material is preferred but it must be placed carefully so that none projects into the lumen lest it act as a nidus for precipitation of cholesterol and bile salts. Some type of support must be furnished the suture line. The authors prefer a T-tube which is inserted through an opening at least ½ inch distal to the suture line, because insertion of the tube through the suture line tends to encourage recurrence of the stricture. (See Fig. 2.) A Penrose drain is inserted down to the duct as the wound is closed.

2. Stricture of the Distal End Only. — Several types of repair are available when the stricture involves the distal end of the common duct. The one preferred by the authors is a side-to-side anastomosis utilizing a longitudinal incision in the common duct as well as in the duodenum (Sanders[2]). In this anastomosis a double row of sutures is necessary; we prefer interrupted catgut for the inside row and interrupted silk for the outside row.

The common duct can be transplanted into the duodenum; however, the authors have not had very satisfactory results with this type of anastomosis.

When more than 2 or 3 centimeters of common duct are present, the authors are of the opinion that anastomosis of the duct to a functioning loop of intestine can be done without much danger of suppurative cholangitis resulting from reflux of food. There is apparently much less danger of cholangitis from reflux in this type of case than when no common duct is left, because the stump of common duct appears to act as a reservoir protecting the intrahepatic bile ducts.

3. Stricture of the Proximal Portion of the Common Duct.—In this type of lesion the repair becomes more difficult. If possible, effort should be made to *find the distal end* of the common duct, as emphasized by Cattell,[3] who actually splits the head of the pancreas in an effort to find it. If the distal end can be found, the duodenum and head of the pancreas can almost always be mobilized sufficiently to bring the distal end of the common duct up to meet the hilar duct, even though only a very short stump remains. In this situation, an end-to-end anastomosis is usually performed, as previously described, inserting a T-tube through an opening distal to the suture line so that the suture line may have support for as long as three or four months, thus minimizing the chance of recurrence.

4. Absence of Entire Duct. — This type of defect is the most difficult one of all to repair, and in general, results are not as good as in the lesions previously mentioned. The authors agree with Allen[4] and others that the use of a Roux Y arm of jejunum is superior to

anastomosis of the duct to a functional loop of intestine because reflux of intestinal content is so poorly tolerated by the liver when the stump of duct is so short that food regurgitates readily into the intrahepatic ducts. The authors proved to their own satisfaction that regurgitation of food could be a factor in production of chills and fevers, although stenosis *is the more common factor.* In two patients on whom we anastomosed a loop of jejunum to the hilar duct, the patients continued to have chills and fever which, however, were abolished completely several months later by section of the proximal arm of jejunum, thus preventing regurgitation. In bile duct repair, the credit for the use of the arm of jejunum designated as the Roux Y arm, should actually be given to Monprofit,[5] who recommended it in 1908.

Use of Mucosal Graft from the End of Jepunum—This procedure is a modification of one recommended several years ago by Hoag.[6] He suggested the use of a flap of gastric mucosa to be inserted up into the strictured area at the hilus of the liver. In view of the experiments of Price and Lee[7] showing that gastric secretions can actually digest, or seriously damage normal living tissue, we have modified this procedure by utilizing the end of the Roux Y arm of jejunum in the graft. This operation is designed primarily for strictures at the hilus of the liver, which is mentioned previously, as unquestionably the most difficult ones to repair from the standpoint of freedom from recurrence. After the Roux Y arm is constructed, the serosa and muscularis is separated from the mucosa and submucosa by sharp dissection for a distance of 2 or 3 cm., as illustrated in Fig. 3. This allows procurement of a tube of mucosa which can be inserted up into the strictured area, thus acting as a graft over the scarred area. After 2 or 3 cm. of mucosa are isolated, a portion of the bell end of a catheter (No. 10 to 14) is cut off and anchored with 2 or 3 sutures of interrupted silk or cotton in the lumen of the mucosal tube. It may be necessary to trim a portion of the mucosal tube, as illustrated in Figs. 3e and 3f. The cuff of mucosa is made long enough to extend through the scarred area in the liver up to normal mucosa of the bile duct, and is anchored in position by 2 silk sutures inserted from the outside into the depth of the duct opening, through the cuff of mucosa, and back through the interior of the opening to the exterior. When these sutures are pulled tight, the mucosal cuff is thrust snugly into the opening, thus producing a water tight closure or anastomosis.

At times considerable difficulty will be experienced in finding the dilated duct at the hilus of the liver. On several occasions we have been unable to find any external duct, but have encountered the duct by aspiration, as illustrated in Figure 3a. An opening is made into the duct by incising alongside the needle with a sharp bistoury. This opening is enlarged by blunt or sharp dissection, making effort to locate any adjacent vessels by aspirating around the opening with a hypodermic needle and

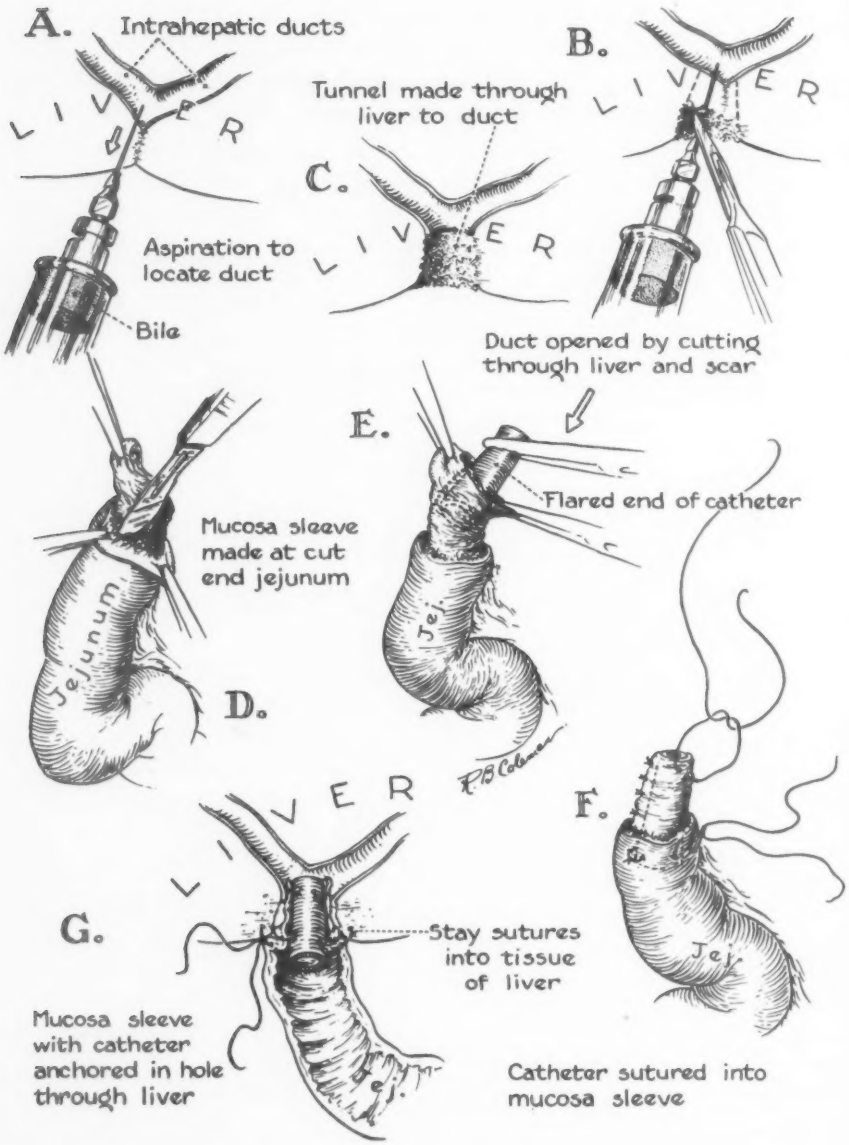

FIG. 3.—Repair of stricture of common duct by preparation of a mucosal tube and the implantation as a graft into the duct opening at the hilus of the liver (modification of Hoag operation). This procedure is most applicable when no stump of duct remains, and scarred liver tissue must be incised to reach the duct. The depth of the scarred area is exaggerated to better illustrate the method. The mucosal tube is pulled into position and held there by two sutures, each of which is inserted from the outside into the depth of the opening, through the mucosal sleeve, and back through the depth of the opening to the outside where the two ends of each suture are tied together. From Cole, in Canadian Med. Assoc. Journ. In press.)

syringe. The opening so obtained usually extends through scarred liver tissue. In our opinion about the only hope of preventing reformation of a stricture at this point is to fill in the defect with a bridge or graft of mucosa. It would no doubt be satisfactory to insert the entire end of jejunum into the opening, but the opening is usually so small that one can get no more than the thin cuff of mucosa, as described above, in the

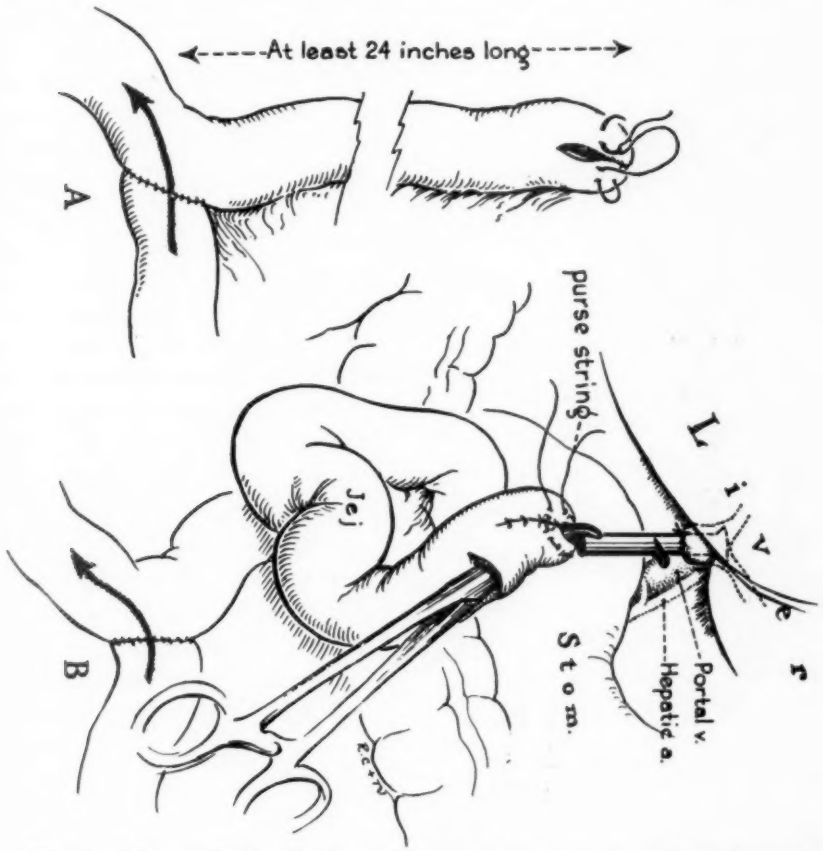

Fig. 4.—When utilizing the Roux Y arm of jejunum to replace the common duct, the ileum is severed about 18 inches from the ligament of Treitz and the proximal end sutured to the distal loop at least 14 inches from the point of severance; the distal end is closed with a continuous suture as shown in A. The end of the vitallium tube is inserted into the end of the intestine, aided by a hemostat through a puncture wound two or three inches from the closed end as shown in B. The end of the Roux Y arm of jejunum is anchored to the liver by interrupted silk sutures. (Modified from Cole, Ireneus and Reynolds, in Annals of Surgery, 1945.)

hole and still have room for an adequate lumen. Since this opening at the hilus is usually funnel shaped, even compression is best obtained by utilizing the flared end of the catheter, placing the smaller end upward into the opening. The wall of the jejunum is anchored in position against the hilus of the liver with three or four interrupted sutures of silk or cotton. In our experience the sutures anchoring the tube in the sleeve

of jejunal mucosa will tear out in three or four months, thus allowing the rubber tube to pass.

Use of Vitallium Tube.—The technic using a vitallium tube in the method of repair utilizing the Roux Y arm of jejunum has been described previously by the authors.[8] The important features in this procedure consist of anchorage of the vitallium tube (see Fig. 4) in the hilar duct, turning in the end of jejunum, inserting the distal end of the vitallium tube into the arm of jejunum and suturing the end of jejunum to the hilus of the liver. Although we originally inverted the end of the arm of jejunum and anchored the vitallium tube with a purse-string suture, we are more inclined in recent cases, when utilizing the vitallium tube, to anastomose the cut edge of the arm of jejunum to the outside edge of the hilar opening without inversion of the end or formation of a cuff (Fig. 5). In the cases in which we have not anchored the vitallium tube with a purse-string around the neck of the tube we have adopted the principle of anchoring it against the wall of the hilar opening with one silk suture through the flange, and another silk suture around the neck of the tube. Our experience with this type of suture in a few cases indicates that the tube remains in place about three months. In our opinion it is not entirely desirable to have the vitallium tube remain longer than six months because such a high percentage of tubes will block if they remain in position longer than this interval.

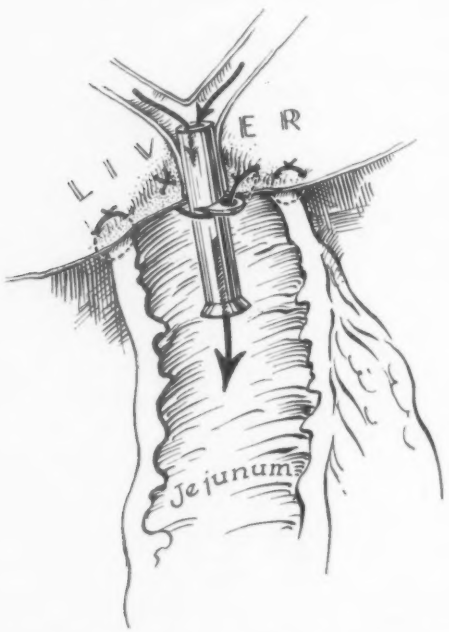

Fig. 5.—An alternate method of suturing the end of the Roux Y arm of jejunum to the hilar duct when the duct protrudes at the hilus is to suture the end of jejunum as near the duct as possible with 4 interrupted silk sutures, without everting or infolding the edge of intestine. In the author's opinion, this type of attachment may minimize recurrence of stricture slightly more than the method illustrated in Fig. 4, although a true mucosa to mucosa anastomosis is not possible with either method. Mucosa to mucosa approximation is possible with the method illustrated in Fig 3, and in the method shown in the above illustration if a wedge of the end of intestine is resected as shown by the dotted line through the mucosa of Fig 3E; the edges on the side of the intestine are then turned in to prevent leakage. The mucosa of the conical shaped end of jejunum thus formed can then be anchored directly to the mucosa of the hilar duct.

Use of a Rubber Catheter.—Use of a rubber catheter to support the suture line when anastomosing the hilar duct to the Roux Y arm of jejunum has previously been described by Allen.[4]. An opening is made

in the catheter to allow bile to drain through the upper end at the hilus downward into the jejunal arm and also to the exterior through the lumen of the catheter. Allen recommends that this catheter be left in place at least three months.

On a few occasions we have utilized a short piece of rubber tube to support the suture line, leaving it in position at the anastomosis but anchoring it in place with a silk suture leading out to the exterior (McArthur[9]). At the end of 3 or 4 months the anchoring suture is cut, thus allowing the rubber tube to pass on out into the intestine.

MISCELLANEOUS TYPES OF REPAIR

We have abandoned the anastomosis of the hilar duct to the duodenum primarily because our results were so poor that other procedures appeared more desirable. We are aware of the fact, however, that a few of our surgical friend are still using this procedure and apparently are having reasonably good results.

Several years ago, we anastomosed a loop of jejunum to the hilar duct in 5 patients, doing an enteroenterostomy between the arms of jejunum about 12 inches from the stoma at the hilus. We have had such poor results with this method that we have abandoned it. We were unable to prevent regurgitation of food up the ascending arm of jejunum into the liver even though a wide enteroenterostomy was performed between the two arms of jejunum. If ample time is taken by the roentgenologist in studying the barium flow in these cases, regurgitation into the intrahepatic ducts will be demonstrable unless folds or valves are made in the ascending arm, as described by us[8] a few years ago.

Although an anastomosis of the gallbladder to the duodenum or jejunum is a satisfactory operation in patients having inoperable carcinoma of the head of the pancreas, we believe the procedure is not advisable in benign lesions because of the regurgitation of food and intestinal secretions into the gallbladder. If an enteroenterostomy is performed, placing folds or valves in the ascending arm of jejunum will prevent regurgitation (Peterson and Cole[10]). If the patient has an inoperable carcinoma, these precautions are probably unnecessary since he will probably die of his carcinoma before the infection becomes serious.

RESULTS

Results of 63 operations performed in 49 patients by us in the past 10 years are summarized in Table II. In 28 patients upon whom we performed an operation suturing the Roux Y arm of jejunum to the hilar duct we had good to excellent results in 78 per cent. In 22 per cent of this group the operation was a failure. Vitallium tubes were used in about 75 per cent of patients having this type of operation. In 4 patients we used a modification of the Hoag procedure, utilizing the

mucosa at the end of the arm of jejunum to graft over the raw area of scarred liver as shown in Figure 3. Good to excellent results were obtained in 3, or 75 per cent of this group. In two of the patients, we were unable to find the dilated duct at the hilus, but encountered it 2 or 3 cm. from the hilus at a depth of 1½ inches from the liver surface. We made an opening alongside our needle spreading the opening by blunt dissection until we were able to insert the mucosal end of the jejunum as a mucosal graft. One patient progressed satisfactorily for 3 months but the stricture recurred shortly after this and she died a few weeks

TABLE II.—*Summary of Results in Repair of Strictures*
(63 Operations in 49 Patients*)

Type of Operation	*No. Op.*	*Results*** (*Exc. of deaths*)	*Op. Deaths*
Hilar duct to Roux Y (75% vitallium tubes)	28	78 good to exc. 22 failure	0
Hilar duct to mucosal flap jejunum (modified Hoag op.)	4	75% good to exc. 25% failure	0
Repair local stricture	7	86% good to exc. 14% failure	1
Hilar duct to duodenum	7	14% excellent 28% fair 58% failure	0
Miscellaneous types of operations	17	60% good to exc. 40% failure	3
Summary	63		4

OPERATIVE MORTALITY RATE 6%

* Not counting one patient in whom no type of repair was possible because no duct could be found at the hilus.

** In 3 cases less than 1 year has elapsed since repair. One of them is already listed as a failure; the results in the other two (good to excellent) cannot be considered permanent because of the short period since operation.

later. The other patient had recurring attacks of jaundice and chills for a few months, but for the past several months has had no difficulty except for an icteric tint in the sclera. The prognosis in conditions as described in these two patients would obviously be poor regardless as to what operative procedure was utilized. The series is too small to give us an index as to the value of the procedure, but at present we believe it offers the best chance of preventing recurrence when the stricture is located at the hilus.

In 7 patients we repaired a local stricture by excising the scarred area and doing an end-to-end anastomosis or a plastic repair of the Mikulicz type. One of these patients died about 10 days after operation. The remainder had good to excellent results.

On seven occasions we anastomosed the duodenum to the hilar duct. In

only one of these (14 per cent) was the result good or excellent. In 28 per cent results were listed as fair, and in 58 per cent were listed as failure.

In 17 patients we performed miscellaneous types of operations which in general yielded very poor results. Most of these operations were performed before we adopted the procedure utilizing the Roux Y arm of jejunum. In this group of miscellaneous types of repair, results were considered good to excellent in only 60 per cent.

In 1946 Pearse[11] summarized the results of numerous surgeons working in this field, and reported that results were considered good in 80.1 per cent of 106 patients in whom a vitallium tube had been implanted in a loop of jejunum for repair of stricture. He reported that in 79 patients the vitallium tube had been used to support a suture line attaching the hilar duct to the duodenum itself; in 42.8 per cent results were considered a failure. We concur in the conclusion that this procedure is undesirable and have used the vitallium tube to support the suture line between the hilar duct and duodenum in only one case. Pearse reported that recurrence of symptoms caused by blocking of the vitallium tube occurred in 11.3 per cent of his combined series.

In our series of 63 operations we had 4 deaths, representing a mortality rate of 6 per cent. Cattell reports an operative mortality rate of 13.8 per cent in 164 operations on 123 patients. Flickinger and Masson reported a mortality rate of 12 per cent in their series of 188 cases.

SUMMARY

In our series of 49 cases of stricture of the common duct we noted that operative trauma was a direct cause of the stricture in 65 per cent. As expected, the best results (86 per cent good to excellent) were obtained in local stricture which was repaired by end-to-end anastomosis. The next best results (78 per cent good to excellent) were obtained in the group having anastomosis of the hilar duct to a Roux Y arm of jejunum.

The most difficult type of stricture for repair is the one in which no duct whatsoever can be found, except at the hilus. In this type of stricture we are convinced that the use of the Roux Y arm of jejunum in bridging the gap represents the best type of operative repair. Although we have had fairly good results with the vitallium tube in supporting the stricture line in such cases, we have recently adopted a new technic, particularly when the stricture is located at the hilus. This method is a modification of the Hoag procedure. Instead of the mucosa of the stomach, we utilize the mucosa of the end of the Roux Y arm of jejunum to act as a graft in covering up the raw area of scarred liver at the hilus. This scarred area at the hilus (present when no stump of duct is found) represents the point where recurrence is most apt to take place. In our opinion, the recurrence rate will be high in those cases unless the area can be covered with a tissue which will minimize scar formation; covering the area with live mucosa of the jejunal arm should offer a better method of eliminating scar forma-

tion, although our series of patients with repair of this type is too small to allow conclusions as to results.

Extreme effort should be made to find the distal stump of common duct which allows end-to-end anastomosis in practically all cases, thus preserving the sphincteric action of the ampulla of Vater.

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DISCUSSION.—DR. ALFRED BLALOCK, Baltimore: Dr. Cole is to be congratulated on his excellent results in this type of difficult surgery. I arise to speak briefly of a method which Dr. William P. Longmire of Baltimore has developed in the laboratory, which has been used by him on several patients. Dr. Longmire would be the first to insist that this method should not be used except in those instances in which the more orthodox procedures, as described by Dr. Cole, have been attempted.

These patients usually have had repeated operations attempted. An incision is made which approaches the left lobe of the liver, thereby avoiding troublesome adhesions which are usually present on the right. Mattress sutures are placed in the left lobe of the liver and a wedge-shaped rather large piece of liver removed until one encounters a dilated duct which is seen at this point. A small area of liver surrounding the duct is removed. One may bring up a loop of jejunum and suture the mesenteric border of the jejunum to the lower edge of this denuded liver segment. An opening is made in the jejunum and an anastomosis is made between this opening and the end of the dilated duct. This shows the completed procedure with the jejunum sutured to the liver.

The first such operation was performed by Dr. Longmire about 14 months ago on a patient who had a traumatic stricture of the common duct. Previous operation had been attempted on several occasions. There had been considerable elevation of serum bilirubin and this fell during the postoperative period, not entirely to normal but it approximated normal. The jaundice disappeared.

Dr. Longmire has used this procedure on three patients to date and the results are encouraging. In a patient operated upon last week the dilated duct on the left was really tremendous—at least a centimeter in diameter—and a very good anastomosis was performed. He has attempted it on several patients who have congenital atresia of the bile ducts, but in cases thus far he has not found a suitable dilated duct.

DR. FRANK H. LAHEY, Boston: I think it is well worth while, even though we have all discussed strictures of the bile duct again and again, to go over the subject again and again because everyone's results with this condition are far from satisfactory. I do not care what method you use to reconstruct injuries to the bile duct, they are in general makeshift procedures. A great many of them do not work or work only for a time and have to be done over. It makes no difference what type of tube you put in; if there is a defect in the duct and you do not get the ends together, most of them will eventually plug, require removal and the insertion of another tube. These operations are trying and tedious, and one does not have the gratifying reward that so often goes with other types of trying and tedious surgical procedures. Many of these patients eventually become jaundiced and get into trouble again.

For these reasons it is, I believe, valuable to discuss the various methods and, as in previous discussions, we wish again to speak of one which has given us the best results of all types of repair of these ducts. In any repair of an injured bile duct we have learned that one of the most important factors is the preservation of the sphincter of Oddi. Without the sphincter there will be a high percentage of cases that will have frequent ascending infection and undesirable jaundice and chills.

The other factor which we have learned in an experience now with more than 200 of these cases of duct repair, is that to get a satisfactory result one must have mucosa-to-mucosa anastomoses. We have learned that the introduction of tubes is a truly makeshift procedure and that while, as stated above, many of them will work, in spite of what has been said about them many will fail over a long period of time.

The principal method which Dr. Cattell and I have developed and discussed at various meetings is the demonstration and liberation of that portion of the common duct which runs through the head of the pancreas and is behind the duodenum where it is always protected from injury. We have learned from operations on the head of the pancreas and from dealing with many duodenal ulcers adherent to the common duct, that by rolling the duodenum to the left and splitting the head of the pancreas, a long section of uninjured common duct can be found. It is possible to so mobilize this that in many of the cases the freed lower end of the common duct can be brought up to where it can be approximated without tension to the lower end of the hepatic duct, and a direct mucosa-to-mucosa, end-to-end anastomosis can be done. In constructing these ducts it is necessary to support the anastomosed duct and to ensure patency of the tube while accurate healing is taking place. For this reason we have introduced a T-tube and left it in place for several months. It is important that this T-tube not be introduced through the suture line but either above or below, so that one arm passes through the anastomosis, and when it is withdrawn it leaves no defect in the suture line. This operation is not applicable to all cases, because many of the patients have been operated on several times and so much hepatic duct has been destroyed that a satisfactory upper end for anastomosis cannot be found. When it is applicable it is, in our opinion, the most useful and most dependable of all methods in terms of long-standing patency.

Another thing that we have learned about repair of injured ducts is that they should be attacked promptly. We used to wait until the patient had developed external sinuses, but we have now learned that the ideal time is while structures are still soft, pliable and movable, and that many times better results can be obtained then, than when, as a result of delay, cicatrization, fixation and distortion of the anatomy have occurred.

We would strongly urge that if repair is to be undertaken on injured ducts, that is, ducts that are known to be injured, it be done as soon as possible after operation. The operation is messy and oozy, and the structures are much more satisfactory to deal with at this time, but it will make possible better restoration of the ducts than will be possible at a later time.

As to the tubes themselves, I do not believe any interpretation of what the end results are will yield dependable figures unless they are observed carefully over a considerable period of time. Many of them drain satisfactorily for a year or two, only to plug eventually.

Personally, I do not like inflexible tubes such as vitallium. In my opinion they have no greater likelihood of maintaining patency than do rubber tubes and they have the great disadvantage of producing pressure and not adjusting themselves to the tortuous tracts into which they must often be inserted. No matter what type of tube we have used, many of them have had to be taken out and another tube inserted within three years because of their becoming plugged with bile salts.

It is, of course, trite to say that if one thinks only of the number of gallbladder operations done each year in the country, one realizes the exposure to the possibility of duct injuries and the very distressing surgical complications which go with them. It is so rightly said by everyone discussing this subject that the best approach to it is to teach that surgery of the biliary tract is dangerous surgery and must be done with good exposure, under good light and with accurate anatomic demonstration of every detail.

Dr. Herman E. Pearse, Rochester, N. Y.: I think it is interesting to note that Elliott, in a presentation before this Association found 26 per cent successful results. Now, though we have different methods and personal preferences our score has risen to approximately 80 per cent. That is worthy of comment. I am inclined to agree with Dr. Lahey that the best way to repair the damage is by direct end-to-end anastomosis. If one can reconstitute the patient's anatomy the way God made him, one will have better physiologic function. However, I have no quarrel with the Roux type of procedure and use it when necessary.

Contrary to the opinion of some, I have no stock in vitallium. I have tested out most of the available materials and have found that vitallium is the best for this purpose. It has faults and so I am searching for a better material.

The final point is that in the Roux type of biliary anastomosis, for which we should give credit to Allen Whipple for popularizing, the best length of the antiperistaltic loop has never been accurately determined. Dennis used a 24-inch loop. I was inclined to use a 10- or 12-inch loop. These patients were studied under the fluoroscope and it was found that the barium would reflux up that loop approximately six inches. In spite of this, some develop cholangitis with a ten-inch loop. Recently, in conjunction with Dr. Radakovich, we have found in dogs that the minimum length for protection is 12 inches.

Dr. Warren H. Cole, Chicago (closing): I wish to thank the discussants for their valuable contribution to this subject today. I believe the method presented by Dr. Blalock and Dr. Longmire has splendid possibilities and should be tried when the duct cannot be found at the hilus. About a year ago I tried a modification of their

procedure on an infant with congenital artresia of the bile duct, but even though I amputated the entire left lobe I could not find a dilated duct to use in any sort of anastomosis.

Dr. Lahey has emphasized the importance of obtaining a mucosa-to-mucosa approximation whenever possible. However, on certain occasions a true anastomosis of this type cannot be accomplished.

In closing, I wish to emphasize that we should find the distal end of the common duct if at all possible, because the sphincter of Oddi is an important structure which the surgeon cannot duplicate.

THE QUANTITATIVE AND QUALITATIVE CONTROL OF BILE FLOW AND ITS RELATION TO BILIARY TRACT SURGERY*

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Cholecystectomy will give satisfactory results in 80 to 90 per cent of the cases where stones are present provided adequate effort is first made to establish a correct diagnosis of gallbladder disease. When cholelithiasis is not a part of the pathologic picture, satisfactory results approximate 60 per cent. In this latter group without stones, the error probably occurs because of a greater incidence of the nervous element, incorrect diagnosis and additional gastrointestinal disturbances, while in the former group, remaining common duct stones or debris are the most common causes for unsatisfactory results. Certainly spastic or atonic conditions of the choledochal sphincter play a role in the post-cholecystectomy syndrome and these conditions may be associated with bile stasis and infection.

The elusive remaining common duct stone is known to every surgeon. No doubt many stones which are found in the common duct at a secondary operation were present in the common duct at the time of the first operation. Nevertheless, the surgeon has an escape when it is appreciated that 7 per cent of all cases of cholelithiasis have stones in the liver and these may be the source of the common duct stones removed at the second operation. This incidence of hepatolithiasis was reported by the writer[3] in 1944. Stricture of the common duct may interfere with bile flow through the common or hepatic ducts, particularly if the bile is quite viscous because of hepatic disturbances or if infection and inflammation are present along the bile ducts. It is my belief that following cholecystectomy or choledochostomy, not infrequently thick inspissated bile, collections of mucus, blood clots, debris and fine particles of precipitated cholesterol or calcium bilirubin are present in the common duct. No doubt many times these move out of the ductal system with return of normal bile flow, but likewise it has been proven by direct observation that such substances may remain in the common duct, and these may be the nucleus for development of common duct stones later on (Figs. 2 & 3). The conditions just reviewed are also factors to be seriously considered when reconstructive procedures are done to re-establish the flow of bile into the intestinal tract.

It is logical to assume that if we could qualitatively control bile flow we should be able to prevent development of biliary tract stones. However, regardless of the many interesting studies and researches on this problem, we have not been able to bring the development of such stones under control. However, we do believe that we are able to control bile qualitatively to the extent that we can produce a thin, watery bile which is less conducive to

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stone formation along the ductal system after cholecystectomy, and can provide a type of bile that flows more readily through the ductal system, particularly if some narrowing of the channel exists. By controlling the quantity of bile, we are able to accelerate its flow and increase intraductal pressure to bring about a flushing out effect.

In discussing bile physiology and chemistry, one must frequently refer to the many studies and publications of Ivy [1, 2, 10, 11] and those who have been associated with him. My own interests have been directed toward the production of a thin watery bile increasing intraductal pressure and promoting relaxation of the choledochal sphincter area in such a manner as to effect a flushing phenomenon of the ductal system. The excellent chemical and physiologic studies of bile by Ivy and his colleagues afford a foundation for any study referable to the quantative or qualitative flow of bile. However, previous to the many studies by Ivy and his group, Neubauer [12, 13] in 1922 and Pohl [16] in 1922 had started investigations on the pharmacological action and therapeutic uses of chemically pure bile acid. Since then many papers have been published on the pharmacodynamic action of various bile acids and bile salts.

Ox bile and pig bile have been used empirically as therapeutic measures for many years. Later investigations proved that ox bile more closely resembles human bile as cholic acid is predominant in both human and ox bile. The essential bile acid in pig bile is hyodesoxycholic acid. Other bile acids are also present in bile and the toxicity of these various acids have been studied by several methods. It was found that by oxidizing cholic acid triketocholanic acid (dehydrocholic acid) was produced. Pure dehydrocholic acid has been proven to be the least toxic of all. The type of bile produced in man and animal by giving oxidized bile acids orally or intravenously is different from that produced by using ox bile.

The salts or acids of glycine and taurine are natural constituents of bile and when bile acid exists in conjunction with glycine or taurine, the term conjugated is applied. The chemically pure bile acids do not contain glycine or taurine.

For the sake of clarity, the various bile preparations most commonly used should be described briefly.

Ox bile is an unoxidized conjugated preparation containing unoxidized cholic acids and some other bile acids in conjugation with glycine and taurine. Oxidation while retaining the conjugation with glycine and taurine results in the oxidized conjugated preparation available under the trade name dechacid. When the glycine and taurine are dropped in the oxidized preparation, an oxidized unconjugated product is formed, consisting of triketocholanic acid (dehydrocholic acid) and di and mono ketocholanic acids. This product goes under the trade name of ketochol. The pure triketocholanic or dehydrocholic acid goes under the trade name of decholin or procholon.

It is possible that with more thorough knowledge and clearer understanding of these substances as they qualitatively and quantitatively affect the bile, we will be able to improve surgical results in biliary tract surgery. This may be accomplished by anticipating certain complications which threaten some operative procedures or correcting complications which have developed by the proper application of our knowledge of bile acid or salt therapy.

Berman with Ivy and colleagues,[1, 2] reported in 1940 on a large group of experiments where various bile acids were fed to dogs with biliary fistulae. The bile volume, water, specific gravity, viscosity, total solids, bile acids (cholates), cholesterol, bile pigment and natural bile salt amounts were studied. Others have also conducted experiments on various phases of this investigation. These studies are consolidated in Tables I and III.

TABLE I.—*Summary of Changes in Bile*
(Berman, Ivy, Doubilet, Best)

	Ox-Bile Salts(1)	Dechacid(2)	Ketochol(3)	Decholin(4)
Bile Volume	+	+	+ +	+ + +
Water	— per/cc.	No change	+ per/cc.	+ per/cc.
Sp. Gravity	No change	No change	No change	No change
Viscosity	+	No change	—	—
Total Solids/cc.	+	No change	—	—
Bile Acids—Conc.	+	No change	—	—
Cholesterol	+	+	+	—
Bile Pigment	No change	No change	No change	No change
Natural Bile Salts	+	No change	No change	No change
Result	Thick bile	Average	**Thin bile +**	Thin bile + +

(1) Ox-Bile Salts — unoxidized conjugated bile acids (glyco & taurocho ic)
(2) Dechacid — oxidized conjugated bile acids (glyco & taurocholic)
(3) Ketochol — oxidized unconjugated bile acids (tri, di & monoketocholanic)
(4) Decholin — oxidized unconjugated bile acids (pure triketocholanic)
Triketocholanic = dehydrocholic

TABLE II.—*Percentage Increase of Normal Bile Flow*
(From Determinations of Berman et al)

	Volume cc. per 24 hours	Total solids per cc/24 hours
Ox-Bile Salts	+ 36%	+ 22%
Dechacid	+ 39%	+ 2%
Ketochol	+ 99%	— 8%
Decholin	+ 106%	— 22%

OxBile Salts — Unoxidized conjugated bile acids (glycocholic & taurocholic)
Dechacid — Oxidized conjugated bile acids (glycocholic & taurocholic)
Ketochol — Oxidized unconjugated bile acids (tri, di & mono triketocholanic)
Decholin — Oxidized unconjugated bile acids (pure triketocholanic)
Triketocholanic acid = dehydrochloric acid

Ox bile salts and dechacid increase bile flow and are choleretics, while ketochol, decholin and procholon not only increase bile flow but produce a thin watery bile and are hydrocholeretics.

It is noteworthy that ox bile salts, which contain glycocholic and taurocholic acid, increase the volume of bile but it is a type of bile with increased viscosity (Tables I, II, IV, V). There is a relative decrease of water per cubic centimeter and an increase of total solids and natural bile salts. Although cholesterol and bile acids are increased, there is no change in the cholesterol-cholic acid ratio so there is probably no increased tendency for cholesterol precipitating and becoming the nucleus for a stone. Likewise,

there is no decreased tendency. No change in the specific gravity or bile pigment values occurred with the use of either the choleretics or hydrocholeretics. The viscosity of the bile produced by these various bile products was measured by the time of flow between two points in a long slender glass tube (Table IV, V). Bile affected by prescribing ox bile is more viscous than normal bile, flows more slowly, and has more difficulty in making an exit through narrow channels. The volume increase as measured by cubic centimeters for 24 hour periods reveals a 36 per cent step up of bile flow (Table II). The total solids per cc. for each 24 hours is increased by only 22 per cent but the viscosity determination reveals the bile to be thicker than normal.

The product dechacid is also conjugated, containing glycine and taurine, but it is oxidized. It is a choleretic as it increased bile volume, but practically

TABLE III.—*Results of Oral Administration of Various Bile Acids in Biliary Fistulae in Dogs (Doubilet)*

Bile Acid Given	Volume of Bile	Total Bile Acids
Normal Excretion	150 cc.	3.37 Gm.
Pure Ox-Bile Salts	265 cc.	8.18 Gm.
Dehydrocholic Acid	510 cc.	4.75 Gm.

TABLE IV.—*Viscosity Determination*
(Berman et al)
Time of flow between two points on a long slender glass tube

	Average Time
Distilled water	1 min. 30 sec.
Control bile	4 min. 15 sec.
Ox-Bile bile	4 min. 50 sec.
Dechacid bile	4 min. 30 sec.
Ketochol bile	3 min. 40 sec.
Decholin bile	3 min. 20 sec.

no other change occurred except a slight increase of cholesterol content which may or may not be of significance. The ultimate result is an increased volume of average type bile.

Ketochol, an oxidized preparation not conjugated with glycine or taurine, effects a larger bile volume than the above products. The water content is increased, total solids are decreased, and it is believed that in general bile acids are decreased. The cholesterol content is increased. There is no relative change in the specific gravity, bile pigment or natural bile salt output, but the viscosity is decreased which results in a thin bile (Table II). Here we find a 99 per cent increase in bile volume, with a decrease in total solids of 8 per cent per cubic centimeter each 24 hours (Table III).

Pure dehydrocholic acid, represented by the products decholin and procholon, results in an increased volume of 106 per cent with a 22 per cent decrease in total solids per cubic centimeter in the 24-hour period (Tables II, III). Bile acid concentration is decreased, and these are the only preparations studied which resulted in a decrease of cholesterol output (Table I). There is no change in specific gravity, bile pigment or natural bile salt

determinations. The viscosity determination is the lowest for this group of choleretics and hydrocholeretics (Tables IV, V).

Doubilet[9] studied the results of oral administration of various bile acids in biliary fistulae in dogs (Table II). It is noted that the normal excretion of 150 cc. per 24 hours increased to 265 cc. with the administration of pure ox bile salts and increased to 510 cc. with dehydrocholic acid. The total bile acids measured 3.37 Gm. for the normal excretion, increased to 8.18 Gm. with pure ox bile salts, and with dehydrocholic acid measured 4.74 Gm.

Our determinations for specific gravity did not reveal changes and with or without bile salt therapy this usually measured between 1009 to 1012. We then turned our attention to viscosity determinations, using long slender glass tubes and clocking the time of flow between two points. Distilled water, natural bile from T-tubes in patients, and bile from T-tubes in patients

TABLE V.—*Viscosity Determinations*
(Best)
Average Percentage Changes in Bile Flow Time

	% Increase	% Decrease
Distilled Water	Control	Control
Control Bile (Natural)	300% over water	
Ox-Bile Bile	10-15% over control bile	
Ketochol		15-20% less than control bile 25-30% less than ox-bile bile
Decholin		20-25% less than control bile 30-35% less than ox-bile bile
Procholon		Same as Decholin

TABLE VI.

Incidence of:	
Common and hepatic duct stones (Crump)	24 per cent
Liver stones (Best)	7 per cent
Choledochostomy (collected series)	9 per cent
Unsatisfactory results—cholecystectomy with stones	10 - 20 per cent

affected by administration of ox bile salts, ketochol, decholin and procholon were studied. We varied the diameter of the glass tubes and made comparative studies with tubes in varying positions (Table V). In these experiments, it took natural bile from T-tubes (control bile) about 3 to 4 times as long to traverse a given length of tube as it did distilled water. When ox bile was prescribed, the bile flow was 10 to 15 per cent slower than for control bile. It must be remembered that control bile from T-tubes varies as it is dependent upon a number of factors, including the liver status. In patients who received ketochol, the bile flow rate was 15 to 20 per cent faster than the control bile and 25 to 30 per cent faster than that of bile following administration of ox bile. With dehydrocholic acid products (decholin or procholon), the bile flow rate was 20 to 25 per cent faster than control bile and 30 to 35 per cent faster than bile following administration of ox bile. It is not difficult to conclude that the thin watery bile resulting from the administration of hydrocholeretics passes more easily through the biliary ductal system, and the amount of bile being increased, it is conceivable that a relative washing or irrigating effect is obtained.

In 1939, the author with several colleagues[4] presented intraductal pressure studies showing that hydrocholeretics increased intraductal pressure by increasing bile flow. The ductal pressure varied with the resistance of the choledochal sphincter area, but in the individual case there was a definite relative increase in the pressure as measured by a manometer under various circumstances. When the hydrocholeretic products were given by mouth, the pressure was increased and sustained for hours or days. When given intravenously, there was a sudden and greater increase in pressure but this was not sustained (Fig. 1).

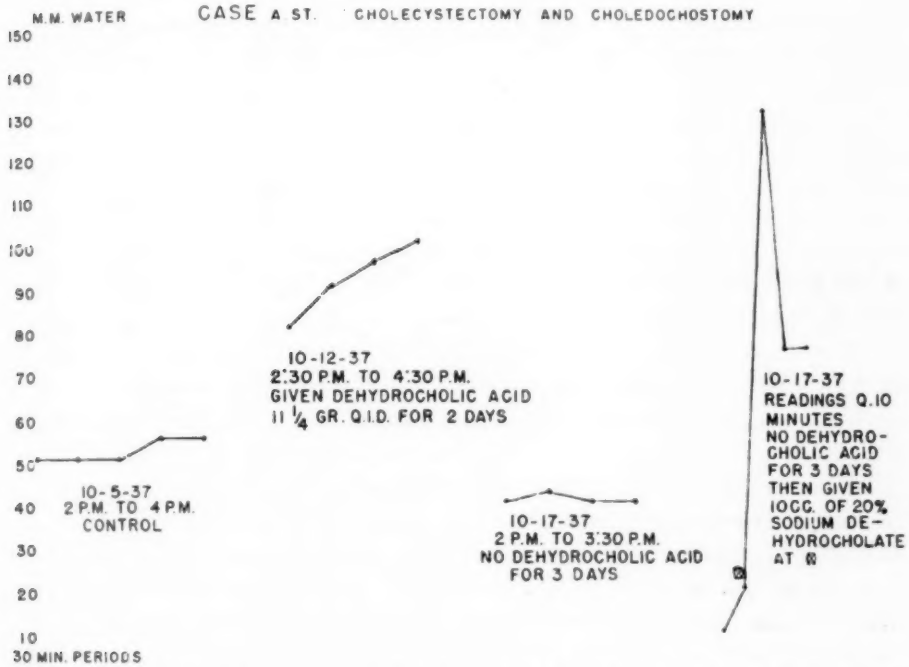


FIG. 1.—Intraductal pressure studies in a patient with a T-tube. Dehydrocholic acid orally results in an elevated sustained intraductal pressure. Sodium dehydrocholate intravenously results in a rapid increase of the intraductal pressure of short duration, but leveling off at a pressure slightly higher than the control pressure.

DISCUSSION

The greater percentage of unsatisfactory results in biliary tract surgery are due to remaining pathology or newly developed pathology in the common or hepatic ducts, most frequently stone or debris. A much smaller group of cases have had injury to the common or hepatic ducts and not infrequently the results of corrective or reconstructive procedures have not been satisfactory. Naturally, other causes exist but are relatively uncommon.

That remaining pathology in the common duct can be a very potent factor is exemplified by the fact that the number of patients with choleli-

thiasis who have stones in the comon duct is much larger than the number of patients whose comomn ducts are explored. This is well illustrated by Crump (Table VI) who reported on his findings in 325 autopsies that revealed cholelithiasis. Of this group, 24 per cent had stones in the hepatic and common ducts, whereas analyses of hospital records rarely reveal that the common duct is opened and explored in one out of four cases of cholecystectomy for cholelithiasis.

One hundred hospital records in cases of cholelithiasis were reviewed several years ago. The surgery was performed by eight different surgeons and choledochostomy was done in only 9 per cent of the cases. My cases were not included because my own incidence of choledochostomy in cholecystectomy cases has varied between 20 and 44 per cent. If only 9 per cent of patients who have a cholecystectomy for cholelithiasis have intraductal exploration and autopsy studies reveal hepatic and comon duct stones in 24 per cent of individuals with cholelithiasis, one can clearly reason that many of these patients must have remaining common duct stones. To further complicate the problem, my own investigations[3] prove that approximately 7 per cent of all cases of cholelithiasis have liver stones. Common duct stones are frequently elusive and escape detection in common duct exploration, only to be portrayed on the postoperative cholangiogram. Liver stones are a more serious problem because of their inaccessibility, and no doubt they may later reach the common duct and give rise to serious difficulty.

From our present knowledge of qualitative control of bile, we probably have little to offer in definitely and completely preventing precipitation or crystallization of substances within the hepatic or common ducts. However, an analysis of collected data (Table I) suggests that a hydrocholetetic consisting of pure dehydrocholic acid (decholin or procholon) not only decreases total solids per cubic centimeter and the viscosity of the bile but also decreases the cholesterol output. According to Berman, Ivy et al,[1] cholesterol does not accumulate in the blood. One could assume then that with less cholesterol available in the ductal system, there would be less opportunity for choleserol precipitation which might subsequently serve as a nucleus or frame for stone development or collect as debris on rubber, vitallium or other substances used in corrective procedures on the common and hepatic ducts.

Pearse,[14, 15] who contributed the use of the vitallium tube in the management of some common duct lesions, presented before this society a year ago an excellent report on the results of the use of vitallium tubes. This was based on the experiences of a large number of other surgeons as well as his own. In three of his patients, when sediment had collected and blocked the vitallium tube necessitating its removal, he took advantage of the opportunity to analyze the sediment. The cholesterol content in the three cases was 38, 36 and 56 per cent, as compared to an average 70.6 per cent cholesterol level in the four thousand gallstones pulverized, mixed and analyzed by Dolkart[8] and his group. In the sediment analyzed by Pearse, the calcium

in the insoluble fraction varied between .0015 Gm. and .0075 Gm. and the remainder was bile pigment. In no case did bile pigment and calcium alone form the sediment blocking the tube. To me, this is an interesting contribution. If it is true, one is warranted in assuming that reduction of cholesterol content will at least be helpful in preventing sediment from collecting. Of course if the bile acid concentration also were decreased below the normal bile acid-cholesterol ratio, precipitation would probably occur but experiments do not reveal unfavorable disturbances in this ratio. Furthermore, if we decrease the viscosity, there is a more rapid flow of bile and precipitate or crystalline sediment is less likely to collect. This is especially true when the bile is a very thin, watery type flowing under increased pressure.

The choleretic, ox-bile salt, increases bile volume by 30 to 40 per cent, while hydrocholeretics increase bile volume 95 to 110 per cent. In corresponding dosages, the pure dehydrocholic acid (decholin and procholon) produces a slightly greater increase of bile flow than the mixture of triketocholanic acid (dehydrocholic acid) with di and mono ketocholanic acid (ketochol). This increased amount of bile flowing through the same size ductal system has a natural flushing or washing effect. There results a natural increased intraductal bile pressure but this may be varied by obstructing agents along the common or hepatic ducts and by the state of spasm or relaxation of the choledochal sphincter mechanism. We have studied the intraductal pressure in many patients with a T-tube in the common duct and have reported some of these studies. We have also studied the amount and type of bile in patients after prescribing choleretics and hydrocholeretics. Of course, many of these studies on the amount of bile flow were not too accurate because part of the bile passed on through the T-tube. However, in one case of complete biliary fistula resulting from common duct injury elsewhere, we catheterized the fistula and were able to collect most of the bile, and an attempt was made to make an accurate estimate of the small amount of bile on the dressings. In a number of other cases where stones almost completely blocked the lower end of the common duct, we believe we had fairly accurate readings on this increased bile flow in humans.

In 1938,[5] a report was made on the removal of remaining common duct stones by means of the biliary flush. We have made no attempt to report all of our successes or failures but in figures 4, 5 and 6, several cases are depicted. A definite regimen is followed, based upon the increased flow of a thin watery bile and the use of antispasmodic agents to relax the lower end of the common duct. Gradually we have collected further data by various studies and wider experience. During the last ten years we have made this flush a routine post-operative procedure in every case of biliary tract surgery. It has also proven particularly helpful in cases where the common duct has been repaired or reconstructed, with or without the use of rubber or vitallium tubes. Likewise it has been of great aid and has lessened our

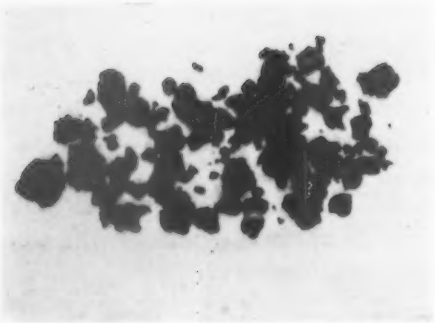


FIG. 2.—Collection of debris or "muck" from a common duct. The smallest particle of cholesterol or calcium bilirubin, if remaining in the common duct, may be the nucleus of a larger obstructing or symptom-producing stone.

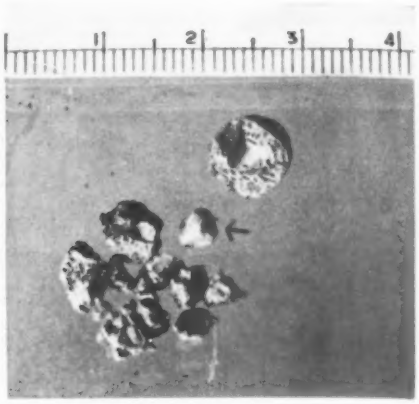


FIG. 3.—The arrow points to a small calcium bilirubin stone of the common duct which was the nucleus for a larger stone resulting in complete obstruction of the common duct. The bed of the small stone can be seen in the larger fragment.

A B

C D

FIG. 4.—Stone could not be located when common duct was explored. Delayed cholangiogram (B) reveals stone at lower end of common duct. After four flushes and six ether-alcohol injections, stone was dislodged (C & D).

difficulties in cases where the hepatic or common duct has been anastomosed to the stomach, duodenum or jejunum with or without the use of rubber or vitallium tubes.

The following regimen is prescribed in all cholecystectomy cases:

1. Three decholin or procholon tablets after each meal and at bedtime for 3 days.
2. One teaspoonful of magnesium sulphate in water each morning.
3. Two tablespoonfuls of pure cream or olive oil before noon and evening meals and at bedtime.
4. On the first day, one nitroglycerin tablet (1/100 gr.) is placed under the tongue before each meal.
5. On the second day, one atropine tablet (1/100 gr.) is dissolved in a little water and taken before each meal.
6. On the third day, the nitroglycerin is repeated as on the first day.

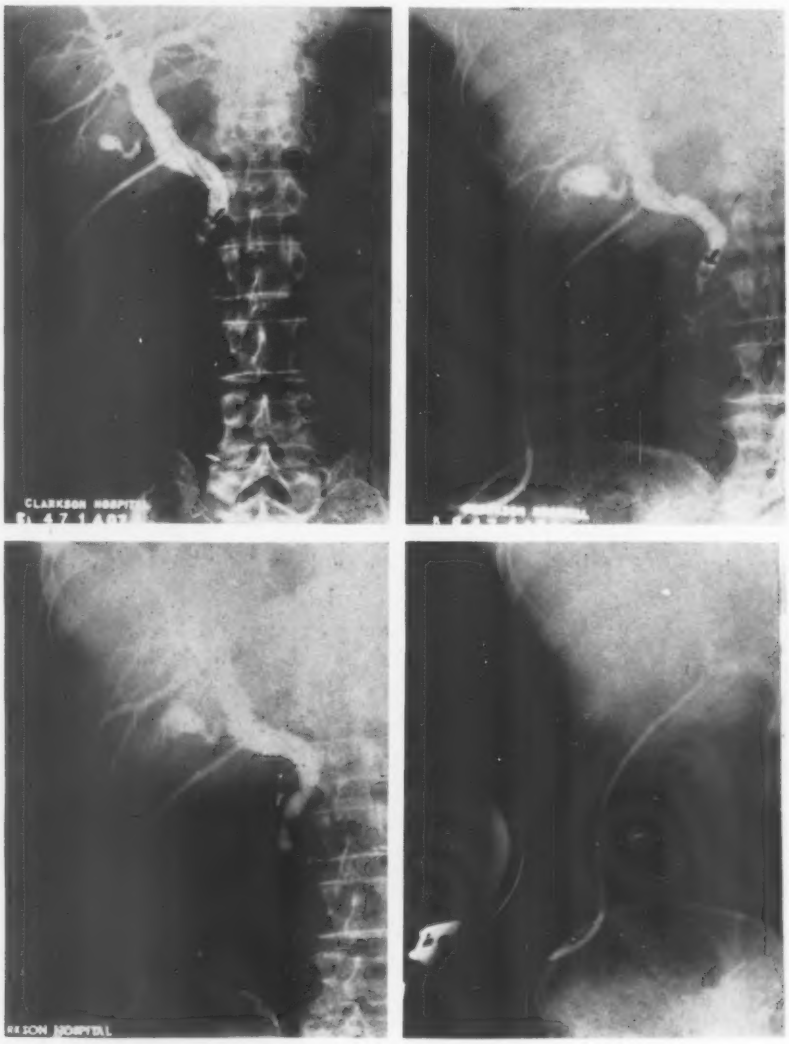
In routine cholecystectomy cases, the flush is started on the seventh postoperative day and is repeated in two weeks. It removes the smaller crystalline or precipitate sediments which may be the nucleus of future stones, and other debris such as mucus, plugs, blood, and the so-called "muck" which we not infrequently see on exploring the common duct (Fig. 2). Also we have repeated evidence that single or multiple small to large stones are dislodged from the common duct.

In 1940, a critical analysis was made of 48 cases of cholecystectomy for cholelithiasis where there had been no indication to explore the common duct. All cases had been operated upon previous to 1936 and had not had the advantage of the biliary flush. Nine patients (18.7 per cent) continued to have symptoms, minor to severe, but definitely referable to the biliary tract. Six of these patients had their symptoms relieved by the biliary flush and two more found out by time and experience that it was necessary to take the flush once each month to avoid recurrence of some symptoms. One case was not relieved, and common duct exploration revealed a stone. Recently I have checked on 60 cases of cholecystectomy for cholelithiasis where there was no indication to explore the common duct and where at least one biliary flush and usually two had been prescribed postoperatively. All of these were operated upon at least one year ago, and a post-cholecystectomy syndrome was present in only four (6.6 per cent). In other words, cholecystectomy was satisfactory in only 82 per cent of the first group but in the latter group, with the aid of the biliary flush, results were satisfactory in 94 per cent of the cases. Three of the latter group are being kept comfortable by taking the biliary flush at monthly intervals. The fourth patient has had several attacks of colic and mild jaundice suggesting biliary dyssynergia or common duct stone. Some relief is obtained by the flush.

The flush regimen is used to dislodge stones in the common duct that are revealed by the routine postoperative cholangiogram (Fig. 4, 5, 6) which is always done in cases of choledochostomy. During the three days of the flush, the T-tube is kept clamped to permit building up of intraductal pres-

sure. Each day the tube is irrigated with warm olive oil after dissolving 1/100 gr. of nitroglycerin under the tongue. If the repeat cholangiogram reveals a stone still present, the same regimen is repeated a number of times. In addition, when necessary, various solvents or substances that will cause fragmentation or dissolution of the stone are injected into the duct. These

A B



C D

FIG. 5.—This patient developed jaundice 26 years after cholecystectomy (elsewhere). We removed several stones from the common duct but delayed cholangiogram reveals a remaining common duct stone (A & B). After several flushes and ether-alcohol instillations, patient was sent home for several months. Upon her return, stone was still present but another flush with ether-alcohol instillation resulted in disappearance of the stone (C & D).

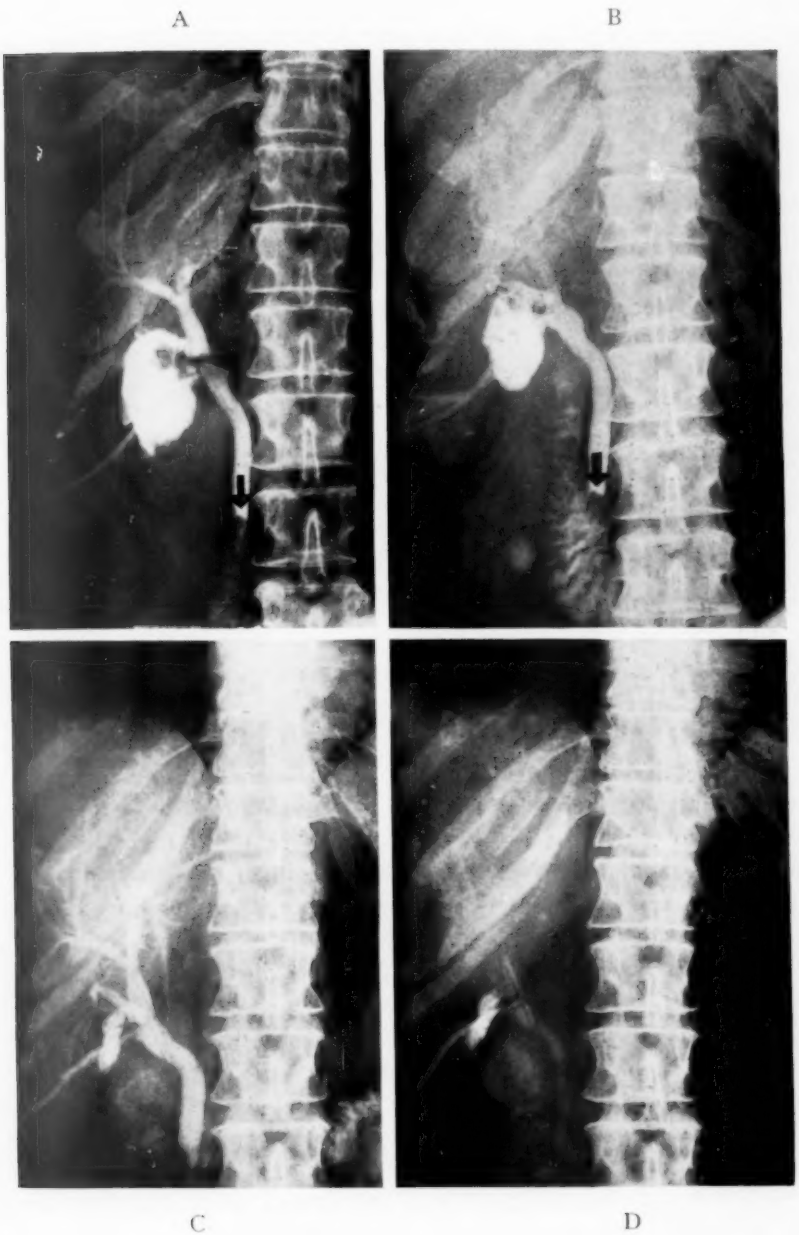


FIG. 6.—Cholecystectomy, with choledochostomy only because of small stones in the gallbladder but no stones found in the common duct. Delayed cholangiogram reveals a stone in common duct (A & B) After three flushes, and without ether-alcohol instillation, stone was dislodged from lower end of common duct (C & D).

include ether-alcohol mixture, chloroform and solution G, which have been previously described in detail.[6] We have had experience in handling our own patients as well as those of other surgeons, and have had reports on other patients whom we have not handled directly, and we believe that success attends about 30 to 40 per cent of the cases where these combined methods are used.

For more than eight years, we have directed every patient who has had a biliary-intestinal anastomosis, with or without the use of a rubber or vitallium tube, to take the biliary flush without the antispasmodic measures once or twice each month. This usually causes any ascending infection to subside and the beneficial effects have been well exemplified by improvement in patients who for some years had presented a serious problem because of chills and fever and frequent mild to moderately severe jaundice. A few patients have made an almost dramatic response, and others have been so much improved as to make the situation compatible with life. At times, the occasional use of the sodium dehydrocholate intravenously over a three day period has been necessary to obtain a beneficial effect. In most of these patients, and particularly where a rubber of vitallium tube has been used, we have recommended taking daily doses of the hydrocholeretic (two tablets night and morning) and taking the biliary flush without the anti-spasmodics once each month. Naturally, we have seen some patients whose improvement has been minimal.

In all cases of common or hepatic duct reconstruction, with or without the use of the vitallium or rubber tube, we place the patient on the complete three day biliary flush the first three days of each month and usually recommend that two tablets of the hydrocholeretic be taken night and morning during the remainder of the month. This regimen takes advantage of the flushing effect and in the interim a thin, watery bile is produced which has less tendency to develop a crystalline sediment or precipitate and flows more readily through any narrowed channel of the ductal system. We do not hesitate to say that in several cases where the vitallium tube had been used and rather serious symptoms developed, this regimen has changed the picture and re-operation has been avoided. It is strongly recommended that this regimen be instituted two weeks after surgery in every case where a vitallium tube has been placed in the common or hepatic duct.

As yet, we do not have complete and satisfactory experimental evidence that we can dislodge intrahepatic stones into the common duct. Theoretically it is a possibility and we have cholangiographic studies revealing stones in the upper hepatic duct becoming displaced into the common duct following the biliary flush. In some of our cases we prescribe the biliary flush previous to surgery.

We are of the opinion that in complete duct obstruction and jaundice, intraductal pressure should not be increased because of possible increased liver damage. There have been several experiments reported that are some-

what to the contrary. Nevertheless, we do not recommend it until some bile is appearing in the stools in cases where no fistula exists.

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DISCUSSION.—DR. HERMAN E. PEARSE, Rochester, N. Y.: I am very anxious to comment on the timeliness of this presentation. The clinical usefulness of the choleretics has been neglected. They are very important and, as our studies of the biliary physiology increase, I am sure that in the future we will have these and other substances that will help in clinical surgery. They are also useful in medicine, for as George Whipple pointed out a number of years ago, if pregnant women are given choleretics just before and after term, there is a great possibility of reducing the incidence of gallstones subsequent to pregnancy. They may also be used in the medical management of the non-calculus type of cholecystitis which, you will agree, is not a surgical disorder in its primary stages.

Choleretics may be used in the presence of occlusion of tubes placed within the bile ducts and in the amelioration of symptoms from such anastomoses as Dr. Cole presented. Such use may avert a failure. Studies on choleretics such as Dr. Best has presented may greatly simplify our management of biliary conditions.

DR. CHARLES G. JOHNSON, Detroit: For some years I have been interested in the study of the bile salt content of bile and its variations. I would like to ask Dr. Best, in relation to biliary flush, what he thinks of the possibility of utilizing it more or less continuously. I have found that if whole bile salts is given, the flow of bile is increased. This material has, in my hands, proved much better in alleviating post-cholecystectomy syndrome than any of the prepared or synthetic bile acids. If I give a patient whole bile and analyze the bile salt excreted through the common duct tube, or if this is done in the animal where one has better control, the first thing that happens is increase in the total amount of bile plus an enormous increase, amounting to practically a quantitative recovery of bile acid administered, if whole bile is given by mouth. Furthermore, if one analyzes the bile acid content of the total amount of bile excreted by the liver, one finds that bile acid is extremely well conserved and utilized. Bile acid will remain fairly high for a week after administration of whole bile. One need not give frequent doses of whole bile to keep the bile acid content of bile high with the associated cholerectic activity. Each time the increased bile comes down into the duodenum one gets additional cholerectic activity from it.

We have been too often in the habit of taking natural material, disintegrating it as much as possible, and selecting one part or another for use. The entire whole bile is preferred to extracted portions, and this can be obtained by addition of water to properly dried bile. It is pretty difficult to make bile, that is, to reconstitute bile from its components. I do not know anyone who has ever done it. Bile is an important material. It seems it makes no difference what type of bile one uses—from the pig or from the human or from the cow—despite the fact that bile salt concentrations, and the type of bile salts, are different in different species. The activity as measured by the sense of well-being of the patient, and the utilization of fat, seems to be just as good with one type of bile as with another.

DR. R. RUSSELL BEST, Omaha, Nebraska (closing): In answer to Dr. Johnston's question, we recommend that the patient have the 3-day biliary flush once each month and then take smaller doses of dehydrocholic acid (decholin or procholon) each day, i.e., one or two tablets only, night and morning. I do not agree that pig bile is as satisfactory as ox bile when whole bile products are indicated for increased flow of a normal or thick bile to aid digestive function. However, Dr. Johnston may have some knowledge on bile experiments that might nullify this statement. The work of Ivy and his associates makes me feel rather strongly at present that ox bile should be prescribed. A dehydrocholeretic product produces a sustained, increased flow of thin bile for at least some four to six days following oral administration. With bile salts the increased bile flow ceases rather early, as it is dependent more upon the amount of actual bile salts absorbed from the intestines. It is this absorbed bile that is excreted. In fact, I recall an experiment where the increase in bile flow was studied and the amount of bile salts (choleretics) administered orally was determined. This cannot be done with the prescribing of dehydrocholic acid products (hydrocholeretics).

I wish to express my appreciation to the discussants.

SPLENECTOMY: WHEN IS IT INDICATED?*

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The subject, when is splenectomy indicated, is automatically divided into three different aspects. The first is the surgical removal of the spleen for conditions directly related to the spleen itself, such as tumors, ptosis, rupture or cyst, to increase radicalness in total gastrectomy or to aid exposure in operations in the left upper quadrant. Secondly, there are those states which have to do with splenic effects upon the peripheral blood cells or upon the bone marrow and the production of red and white blood corpuscles as well as platelets. Finally, there is a third division in which the indications for splenectomy are less well established in terms of lasting benefit from it. This includes the early cases of congestive splenomegaly, and the patients in whom the splenomegaly is of unknown origin and for whom the question arises as to whether or not splenectomy would be valuable as a prophylactic against possible later splenic effects.

GROUP I

The tumors of the spleen, such as lymphosarcoma and Hodgkin's disease that are rarely but occasionally limited, at least in the beginning, in their involvement to the spleen, require no discussion, particularly when it is realized, as will be discussed in a later section dealing with splenic effects on bone marrow and blood, that at any time true tumors of the spleen or infiltration of the spleen as a part of the disease known as Gaucher's disease or inflammation of the spleen can promote secondary bone marrow and blood cell effects, producing the blood condition known as hypersplenism. This secondary splenic effect, associated with tumors and inflammatory processes in the spleen, results in depression of blood platelets, depression of granulocytes and depression of red blood cells. If such splenomegaly results in this state, panhematocytopenia, there can be no reasonable disagreement regarding the wisdom of splenectomy.

We have had four true cysts of the spleen. Since these in no way are difficult to manage, it can be assumed that the indications for splenectomy in these states are likewise accepted by everyone, particularly when such cysts attain significant size.

The wandering spleen with which we have had but one experience, sub-

* Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

ject as it occasionally is, to torsion, likewise falls into the group for splenectomy, about which there would be no debate.

Trauma to the spleen, resulting in rupture and hemorrhage, likewise requires very little discussion. Located, as the spleen is, in the left upper quadrant and possessing, as it does, a definite pedicle also with quite inadequate fixation attachments to the posterior parietal wall of the abdomen, the spleen is subject to injury following any trauma to the left upper quadrant. This may occur even when an indirect force to the pedicle of the kidney results in transmitted effects on the splenic vein and artery as they pass from the tip of the pancreas into the hilum of the spleen.

There is little that need be said regarding the indications for splenectomy in rupture of the spleen except to recall that force or injury which results

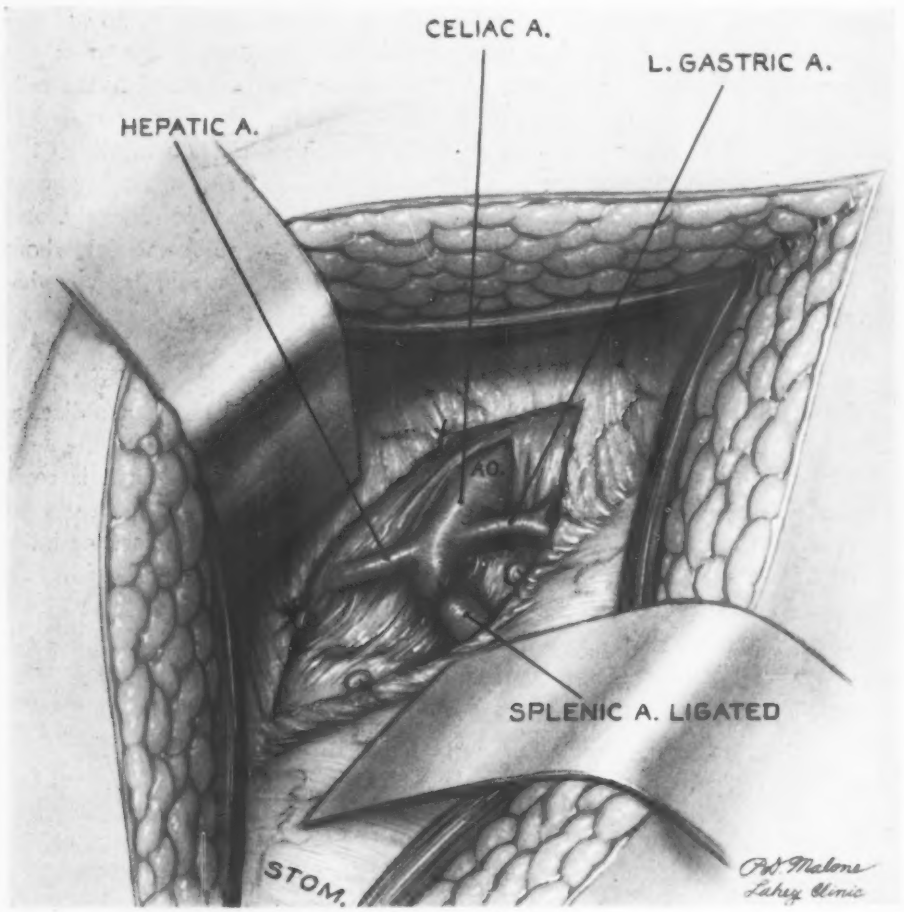

FIG. 1.—This illustration shows the preliminary ligation of the splenic artery close to its origin through the gastrohepatic omentum. This plan of controlling the arterial blood supply to the spleen close to the origin of the splenic artery is valuable, as discussed in the text in those large spleens difficult to displace and in those spleens, limited in number, with perisplenitis in which splenectomy is contemplated.

in rupture of the spleen is delivered also to the pedicle of the kidney. In splenectomies done for ruptured spleen one should always be sure that there is not present also an injury to the underlying kidney.

The type of splenectomy which is done upon ruptured spleen is quite different from the deliberate approach to the pedicle of the spleen when splenectomy is undertaken for splenic effects upon the bone marrow or upon peripheral blood cells as shown in Figure 2. Since the patient will be in a state of relative emergency, the less elegant but much more time-saving procedure of freeing the spleen from its peritoneal attachments by means of

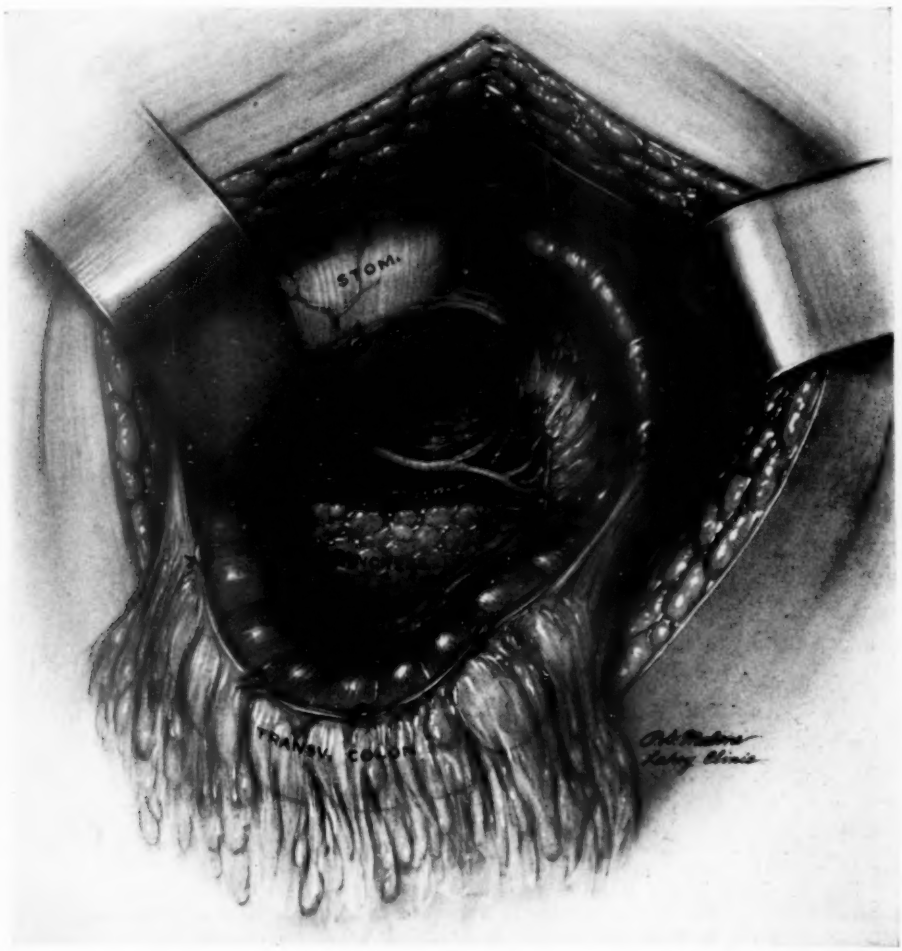

FIG. 2.—This illustration shows the most satisfactory approach to the vascular pedicle of the spleen by wide exposure through the gastrocolic omentum. As stated in the text, by means of this exposure, accurate control of the blood supply to the spleen is obtained and it is possible to make very adequate searches for accessory spleens.

This method of approach was described and illustrated by Dr. Albert O. Singleton, and undoubtedly is employed by many surgeons.

separating it bluntly with the finger, turning the entire spleen upward and inward together with the tail of the pancreas (Fig. 3) and ligating or clamping the splenic blood supply at once, will give immediate control of bleeding, lessen the amount of blood loss, and shorten the time required to do the operation.

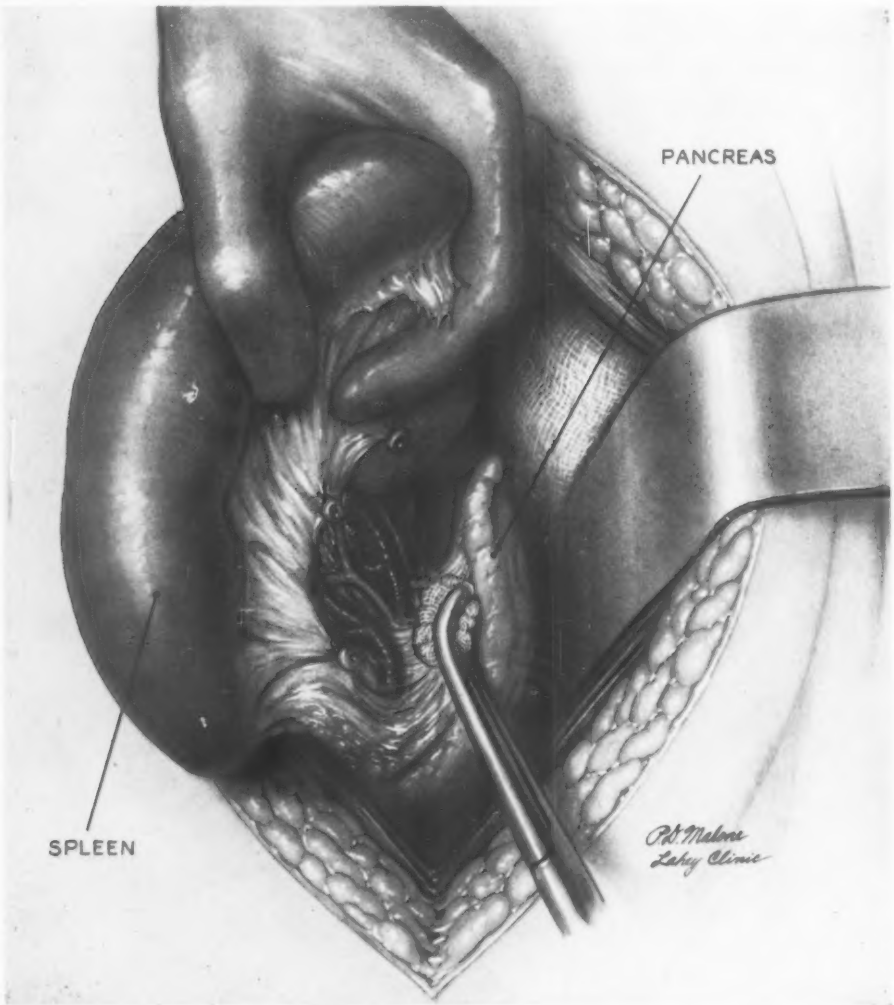

FIG. 3.—This is the standard method for accomplishing splenectomy rapidly by means of which the spleen is bluntly freed from its peritoneal attachments, turned forward into the wound, the tail of the pancreas wiped off and its pedicle controlled by clamps, mass ligature or individual ligature.

With the spleen out, it is not difficult to visualize the kidney region and determine whether or not there has been coincident injury to the renal vessels or to the kidney itself.

There is still another group of cases in which in recent years we have

employed splenectomy. This group includes the cases in which splenectomy, together with omentumectomy, is included in the operation of total gastrectomy in order to make the anastomosis of the jejunum to the esophagus easier, but primarily to increase the radicalness of total gastrectomy when done for early or extensive gastric malignant disease. We have employed splenectomy in about half of the 100 cases of this type in which we have done total gastrectomy.

It will be recalled that in most of the patients for whom total gastrectomy is employed, that is, those with lymphoma of the stomach, those with leiomyosarcomas involving most of the stomach, or those with carcinoma of the stomach of the linitis plastica type infiltrating usually a good part of the walls of the stomach, the malignancy as a rule involves all of the greater curvature and frequently runs upward to the entrance of the esophagus into the stomach. It is obvious that if the spleen be left behind and separated from the stomach by the ligation of the vasa brevia, there will be a section of omentum left behind attached to the spleen, there will be a severing of the blood supply along the upper part of the greater curvature of the stomach quite close to the gastric malignancy, and that by the removal of the spleen and not part but all of the omentum, a much more radical and extensive removal of the malignancy with a wider area about it can be accomplished. For this reason we believe that splenectomy, since it is apparently harmless from our experience with this good sized series of cases in which it has been added to total gastrectomy, is a very desirable procedure to employ in this condition.

There will be other conditions, such as transthoracic resection of the lower esophagus and cardia, also certain patients with diaphragmatic hernia in whom the spleen has migrated into the intrapleural hernia sac, and certain cases of diaphragmatic hernia, repaired from below, in which the removal of the spleen will make the exposure of the diaphragm and suture of the hernia in it much easier. There will even be cases of high ulcers of the lesser curvature in which, by removal of the spleen, a section of stomach can be so rotated downward that the high lesser curvature ulcers close to the esophagus can be removed and an adequate amount of stomach made available by this exposure and rotation to make it possible to do a partial gastrectomy rather than a total gastrectomy. In addition to this, there will be a few diverticula of the stomach high on the greater curvature in which removal of the spleen will make exposure and management of these lesions easier.

GROUP II

It is not as easy to discuss those indications for splenectomy which are related to what has been called the effects of hypersplenism upon the bone marrow and the peripheral blood cells, since hypersplenism may be either primary and of unknown etiology, as in idiopathic thrombocytopenia, idiopathic neutropenia or hemolytic anemia, or secondary as the result of in-

vasion of the spleen by tumor, inflammation or even associated with the splenomegalies of congestive splenomegaly. Those states are in addition much more complex as to the indications for splenectomy since many of the blood states which are caused by hyperspleens can and sometimes are brought about by toxic substances, certain drugs and some metabolic disturbances.

There is an important relationship existing between the spleen and the reticulo-endothelial system on the one hand and the bone marrow on the other. The spleen normally inhibits the bone marrow so as to exert a controlling influence on the output of blood cells produced by it. Under certain circumstances, this delicate balance is disturbed and the spleen may over-

TABLE I—*Indications for Splenectomy*

Group I.
1. Rupture of the spleen
2. Wandering spleen
3. Primary splenic tumors
4. To aid in exposure and radicalness in operations in left upper quadrant

Group II.
1. Congenital hemolytic anemia
2. Acquired hemolytic anemia (selected cases)
3. Idiopathic thrombocytopenic purpura
4. Idiopathic neutropenia
5. Primary splenic panhematocytopenia
6. Secondary splenic panhematocytopenia (selected cases)

Group III.
1. Congestive splenomegaly (selected cases)
2. Splenomegaly of unknown origin (selected cases)

inhibit the various cell-forming functions of the bone marrow or it may destroy cells more rapidly than it normally should. In some cases there is a combination of these two factors at play. These mechanisms are the basis for the indications for splenectomy in certain hematologic abnormalities.

It can no longer be said that there are only two clear-cut medical indications for splenectomy, namely congenital hemolytic anemia and idiopathic thrombocytopenic purpura. We must now add further medical indications: selected cases of acquired hemolytic anemia, idiopathic neutropenia, primary splenic panhematocytopenia, selected cases of secondary splenic panhematocytopenia, selected cases of congestive splenomegaly, and selected cases of splenomegaly of unknown origin (Table I).

Congenital Hemolytic Anemia. The hereditary abnormality in this disease leads to a change in many of the adult red blood cells by which they are

small in diameter but thicker than normal. These spherocytes are removed by the reticulo-endothelial system, of which the spleen is an important part, and their destruction leads to evidence of increased hemolysis with an increased output of urobilinogen in the urine and feces and hyperbilirubinemia. The anemia resulting from the destruction of red blood cells stimulates the bone marrow, which becomes overactive, the hyperplasticity being normoblastic in type. The reticulocytes in the peripheral blood are increased.

Splenectomy stops the greater part of this blood destruction, although it does not change the abnormality leading to the spherocytosis. If care is taken to remove accessory spleens, it is rare to have any return of anemia or jaundice. It is in this condition that splenectomy is most uniformly followed by good hematologic results.

We have had 20 such cases in the period from 1934 to 1947. There were no operative deaths. Three accessory spleens were found and removed in this series. Pigment gallstones were present in 25 per cent of the cases. Splenectomy resulted in complete cure of the anemia in 90 per cent of the cases and marked improvement in the other 10 per cent.

Acquired Hemolytic Anemia. This condidition may be acute or chronic and may be secondary to a large number of diseases. The most important of these are: chemical toxins such as benzol, some parasitic diseases as malaria, certain bacterial infections, some cases of malignancy as leukemia, and idiopathic types in which abnormal agglutinins and hemolysins may be found. It is often impossible to predict whether splenectomy will be of any value in these cases. In general, it should not be done in malignancy, infections or parasitic disease. Rarely, a severe hemolytic anemia in a very chronic lymphatic leukemia might be benefited by splenectomy. Acute hemolytic anemia of the acquired type often responds favorably to splenectomy but does not always do so. The chronic hemolytic anemias demand detailed individual study and in selected cases removal of the spleen may prove beneficial. Results are uncertain, although occasionally spectacular. It should generally be considered the procedure of last resort in these conditions.

We have operated on six such patients (1934-1947), with no operative deaths but with excellent results in only one.

Idiopathic Thrombocytopenic Purpura. This hemorrhagic disease of unknown origin must be carefully distinguished from thromboctytopenic purpura of known cause. All drug contacts must be scrutinized and allergic phenomena considered. It is essential to study the bone marrow where the megakaryocytes in the idiopathic type will be plentiful and will show little platelet formation at their periphery. Bone marrow study will also rule out infiltrating disease, such as leukemia, which may cause thrombocytopenia by replacement. If the eosinophils are markedly increased, allergic types of thrombocytopenia must be suspected. If these precautions are strictly observed and the studies indicate a truly "idiopathic" type, results of splenec-

tomy will be good. However, under the best of circumstances relapses will occur, sometimes many years after operation.

The response to splenectomy is usually immediate but cases have been observed in which it was delayed and slow, although eventually adequate. The increased capillary fragility, prolonged bleeding time and low platelet count rapidly become normal and the purpura disappears. About 75 per cent of patients who undergo splenectomy for this condition remain permanently cured. In acute fulminating cases, splenectomy must be done as an emergency in order to avoid hemorrhage into vital organs. The discovery and removal of accessory spleens are of particular importance in this condition because if thrombocytopenic purpura should recur at a later date, the uncertainty of finding splenic tissue at operation makes any surgical procedure so dangerous as to be prohibitive. We have had 17 cases of this type with no operative mortality. Recurrences have taken place in three cases (17.6 per cent) and in two cases the response of the platelets was slow but eventually good. The other patients all responded rapidly and apparently permanently.

In patients with hemolytic anemia or with idiopathic thrombocytopenic purpura, once splenectomy has been settled upon it should be carried out without undue delay to avoid the occurrence of a critical state which can arise during the delay interval.

Idiopathic Neutropenia. In certain cases when the balance between bone marrow and spleen is upset and the normal inhibitory effect of the spleen is enhanced, the granulocytes alone may be affected, leading to a neutropenia. As in the other hematologic conditions already discussed, careful study of these cases is essential to rule out other known causes of neutropenia, such as drug and other chemical contacts, aleukemic leukemia, lymphoblastoma, and various infections. Again, the bone marrow picture will help to rule out these secondary causes of neutropenia and in the idiopathic type will be normal or will show a hyperplasia of the granulocytic cells with little change in the other elements.

It has only been in recent years that this disease has been established as a definite entity and now takes its place as another form of hypersplenism. The response to splenectomy is immediate and although enough time has not elapsed fully to evaluate this procedure, results appear to be long lasting.

Primary Splenic Panhematocytopenia. This form of hypersplenism involves all of the main cellular elements of the bone marrow and results in neutropenia, anemia and thrombocytopenia. The etiology of this syndrome is not known. Both congenital and acquired types have been described. Bone marrow studies in either type demonstrate hyperplasia involving the red cells, granulocytic and megakaryocytic elements. When the enlarged spleen is removed, there is a rapid return to normal hematologic values in the peripheral blood. Some cases are acute and require emergency splenectomy, while others are chronic and gradually become severe enough to require re-

peated transfusions to sustain life. Splenectomy is indicated in all cases of this syndrome when care has been taken to exclude known causes for panhematocytopenia.

Secondary Splenic Panhematocytopenia. A decrease in neutrophils, platelets and red blood cells in the peripheral blood may be secondary to a number of disease processes. In some way, as yet not understood, a spleen that is involved in almost any disease and becomes enlarged, particularly if the disease be of any lasting nature, may become hyperactive and exert an abnormal inhibiting effect on the cells of the bone marrow with or without an added increase in the destructive processes carried on by the spleen. For instance, Hodgkin's disease may be first discovered in this form when the spleen alone is involved and when the blood picture is only indirectly caused by the underlying disease coming as it does from a diseased spleen. Other forms of lymphoblastoma, chronic malaria, rheumatoid arthritis, congestive splenomegaly, sarcoidosis, tuberculosis, Gaucher's disease, and certain drug sensitivities, as in some cases of benzol poisoning, are all examples of the etiologic factors that may cause this syndrome.

Selected patients in this group respond well to splenectomy, the selection depending on the type of primary condition underlying the process, the severity of the hematologic abnormality, and the probable duration of life in the primary disease. Patients suffering from Hodgkin's disease with secondary hypersplenism of this panhematocytopenic type may rarely have no other manifestations of the disease for long periods of time and under such circumstances splenectomy is justified. This type of problem taxes the physician's judgment severely and it is sometimes impossible to judge whether the duration of life after splenectomy will be long enough to justify the procedure.

We have had seven cases of splenic panhematocytopenia. There has been no operative mortality in this group. The hematologic results have been excellent in four, good in one and fair in two.

GROUP III

Under the third group comes congestive splenomegaly and the splenomegalies of unknown origin.

Congestive Splenomegaly. This condition arises whenever there is a partial or a total obstruction in the splenic vein or any portion of the portal system at or above the level of the splenic vein. Such obstruction results in hypertension within the portal system behind the obstruction and to an engorged collateral circulation that often menaces life by severe hemorrhage into the stomach or esophagus. The most common site of portal obstruction is within the liver itself and is the result of cirrhosis. Other less common etiologic factors in this syndrome are congenital abnormalities of the portal system, rare cases of Schistosomiasis mansoni and thrombosis of the splenic vein. When portal cirrhosis is the primary factor, hepatic failure or hemorrhage from varices may be the terminal event.

In addition to the danger of hemorrhage from varices, the enlarged spleen often eventually leads to panhematocytopenia with its bad effect on the general well being of the patient. Banti originally implied that a splenic hormone was to blame for the liver cirrhosis in these cases and this theory has never been completely disproved. Careful evaluation of the patient with this syndrome is essential and a decision for or against splenectomy is often difficult to make. In general, it should be said that any patient with congestive splenomegaly should have the enlarged spleen removed if he is able to stand the operative procedure. By this means, from 25 to 40 per cent of the blood entering the portal circuit can be removed and the hypersplenic effects of the enlarged spleen abolished. Unfortunately, we often see these patients only after they are far advanced in their disease, and they are often desperate risks. Only after extensive study of the liver function, prolonged medical preparation, and careful weighing of the pros and cons in the individual case can a decision be reached. If we are to help more of these patients, it is necessary that we see them before the late phases of the disease when liver function has been so badly damaged, varices so widely established and secondary hematologic changes so far advanced.

Splenectomy should be performed as soon as the diagnosis has been established and the condition of the patient permits. We have had 25 cases of congestive splenomegaly in this series (1934 to 1947); there have been two operative deaths, a mortality of 8 per cent. These represent the only operative deaths in the entire series. Postoperative complications are frequent and vary from many types of infection to liver failure.

Of the 14 patients who had gastro-intestinal bleeding preoperatively, 12 could be followed postoperatively and three of these had recurrent hemorrhage, one eight months after operation, one three and one quarter years after operation and one three and three quarter years after operation. The course of the remaining nine patients was followed from three months to seven years with an average follow-up of 26 months, and they had no postoperative bleeding. Hematologically, the results have been uniformly good with return to normal blood values.

Splenomegaly of Unknown Origin. Routine careful physical examination will uncover a considerable number of cases of unexplained splenomegaly in the course of any physician's practice. These cases tax his diagnostic acumen and a number will remain unexplained after exhaustive study is completed. If, after six months' observation, the spleen enlarges or remains unchanged and the cause is still unknown, it should be removed. In the temperate zones many cases of early congestive splenomegaly will be discovered in this way, and when removed at this stage will greatly delay or entirely prevent the development of varices. Some examples of malignant tumors primary in the spleen will be found and occasionally removed before spread to other parts of the body has taken place. Removal and study of these spleens undiagnosed before operation will do much to increase our

knowledge of this organ, its pathology and its pathologic physiology. It is understood, however, and this point cannot be overemphasized, that splenectomy must never be performed until all studies have been exhausted in attempting to make a diagnosis and above all, a sincere effort made by a competent observer to rule out definite contraindications to splenectomy.

CONTRAINDICATIONS

It is essential that the spleen not be removed in cases of agnogenic myeloid metaplasia because in this condition much of the bone marrow function of forming blood cells has been transferred from the bone marrow to the spleen and removal of this organ may be rapidly fatal. Competent hematologic study and bone marrow observation will quickly establish this diagnosis and any thought of splenectomy must be dismissed. With rare exceptions, splenectomy in cases of leukemia and lymphoblastoma with splenomegaly should be avoided. The exceptions include rare panhematocytopenias or hemolytic anemias of severe degree caused by hypersplenism in some of these cases. They also include cases in which the disease may still be limited to the spleen but such cases are very rare indeed. The spleen should not be removed in polycythemia vera although rarely a case is seen in which the influence of the enlarged spleen is such as to inhibit the output of a normal number of cellular elements. It is most unusual to find splenomegalies in infections in which splenectomy is justified, although rarely the hypersplenic effect is such as to demand careful consideration of this procedure. In general, patients with paroxysmal nocturnal hemoglobinuria do poorly after splenectomy and patients with Mediterranean and sickle cell anemias are also not helped by the procedure.

The technical complications of splenectomy in patients with congestive splenomegaly in which marked perisplenitis exists are of such seriousness and the benefits so problematical as to contraindicate its employment when this state is found.

COMPLICATIONS

The complications of splenectomy are hemorrhage, thrombosis and infection. Hemorrhage may arise from the surgical bed if a vessel comes loose or it may arise from a general oozing secondary to severe liver damage and a resulting hypoprothrombinemia. This complication sometimes follows splenectomy for congestive splenomegaly associated with severe liver damage and is of bad prognostic significance. Thrombosis occurs more readily after splenectomy than after other surgical procedures because of the rapid and excessive rise in platelets that occurs immediately following operation. Careful observation of the platelet count and the institution of anticoagulant therapy in certain cases will reduce this complication to a minimum. Infection of various types may follow splenectomy particularly in cases of congestive splenomegaly associated with severe liver damage, and in these cases modern potent antibiotics should be used

prophylactically. Liver failure may follow and attempts should be made to anticipate this with present day methods.

Table II demonstrates the frequency of complications in congestive splenomegaly as compared to other reasons for splenectomy. Table III shows the type of complications encountered in our series.

TECHNICAL CONSIDERATIONS

Many methods of doing splenectomy have been developed and published but in general the approach to splenectomy divides itself again into three

TABLE II—*Frequency of Complications of Splenectomy*
(1934-1947)

Congenital hemolytic anemia (20 cases)	1
Idiopathic thrombocytopenic purpura (17 cases)	3
Acquired hemolytic anemia (6 cases)	2
Congestive splenomegaly (25 cases)	19
Cysts (4 cases)	0
Miscellaneous (4 cases)	0
Total	25

TABLE III—*Type of Complications of Splenectomy*
(1934-1947)

Atelectasis	4
Subdiaphragmatic abscess	3
Thrombophlebitis	4
Ascites	2
Hemorrhage from liver failure	3
Miscellaneous infections	7
Hemolytic crisis	1
Diarrhea (question of etiology)	1
Total	25

distinct plans: (1) preliminary ligation of the splenic artery close to its origin; (2) the deliberate exposure of the splenic vessels along the upper edge of the pancreas and as they enter the hilum of the spleen by careful and accurate exposure, as shown in Figure 2, through the gastrocolic omentum and (3) the rapid method of freeing the spleen from its attachments to the lateral and posterior abdominal wall by blunt separation of the spleen from these peritoneal attachments with the fingers. Each of these technical approaches to splenectomy has advantages under different circumstances.

In the spleen of enormous size and in those with any degree of perisplenitis, the method shown in Figure 1 in which the splenic artery is ligated close to its source of origin has great advantages controlling, as it does,

the main arterial supply to the spleen. In those patients with blood changes not in acutely critical states in whom careful and deliberate anatomical exposure can be obtained and in whom, because of their general condition, the matter of time is not important, the method shown in Figure 2 is most applicable. By this plan of visualization, the vascular structures entering the hilum of the spleen can be clearly visualized and individually and accurately ligated. All operations with this exposure can be done neatly in a dry field, and with this exposure, careful search, as is so often necessary, can be made for accessory spleens.

TABLE IV—*Results of Splenectomy*

Disease	No. of Cases	Good	Fair	Poor	Deaths	No follow-up available
Congenital hemolytic anemia	20	18	..	..	0	2
Idiopathic thrombocytopenic purpura	17	13	..	3	0	1
Acquired hemolytic anemia	6	1	..	5*	0	..
Panhematocytopenia	7	5	2	..	0	..
Congestive splenomegaly	25	17	3	2	2	1
Cysts	4	4	..	..	0	..
Miscellaneous	4	2	..	..	0	2
Total	83	60	5	10	2	6

* This group can be improved in the light of our present knowledge and by being more critical in the selection of cases.

In those patients in a more urgent state, such as patients in whom rupture of the spleen has occurred, patients in whom splenectomy must be done for serious blood changes and who are in critical states, the method shown in Figure 3, by which the spleen can be rapidly delivered, the tail of the pancreas separated and the pedicle clamped or ligated, can very materially save both time and blood. This type of splenectomy, however, does not lend itself as well to careful search for accessory spleens as does that shown in Figure 2.

Splenectomy. The operation of splenectomy has now been performed for so many years, so many men have done it and it has been so well standardized that, other than to illustrate these three methods of approach, we do not believe further discussion of the technical considerations of splenectomy are necessary.

We have employed a good sized left rectus, longitudinal, transrectus incision in all of these cases, but realize that tastes in incisions vary and that there is but one point involved in any discussion of them, namely, that they should be of sufficient length to make it possible to visualize the anatomy and to do surgically anatomic procedures.

COMMENT

The decision for splenectomy in any given case is not to be entertained lightly. The operation may be technically extremely difficult and the postoperative path strewn with obstacles. The careful selection of cases is essential. Complete medical and hematologic study will help in this selection. A mistaken diagnosis may put the patient through a serious operation without benefit or an error in judgment cost him his life. Only by the closest cooperation of the surgeon and the internist can the greatest benefit be derived or a catastrophe averted.

With the spreading knowledge of the increased number of indications for splenectomy, the dangers of this procedure may be overlooked and the contraindications misunderstood. This could result in placing a valuable procedure in disrepute.

If our knowledge of splenectomy, its indications and contraindications is to advance, it is essential that the interest of physicians and surgeons be aroused in recognizing splenomegaly in its early stages at a time when the greatest good is to be derived from its removal (Table IV).

SUMMARY

1. We have discussed the three groups of conditions in which splenectomy is indicated.

2. The removal of the spleen to facilitate the ease of total gastrectomy and to increase the radicalness of this procedure is recommended.

3. The hematologic indications and contraindications for splenectomy are discussed.

4. Congestive spleens, when the patient's condition will permit it, should be removed to prevent future complications or to improve such complications if they already exist.

5. Enlarged spleens of unknown etiology after adequate and prolonged study should be removed.

6. The contraindications are specific and must be observed.

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DISCUSSION.—DR. GEORGE M. CURTIS, Columbus, Ohio: In a considerable series of splenectomies for congenital hemolytic icterus and for thrombocytopenic purpura we have had eight recurrences; three in congenital hemolytic icterus and five in thrombocytopenic purpura. The first two have been reported in the Annals (Vol. 123, p. 276, Feb. 1946). In the third patient, with thrombocytopenic purpura, there was a definite recurrence after two years. An exploratory operation was done and no accessory spleen was found in the ordinary or even in the unusual places. As a consequence we recalled the embryology of the spleen, which develops from the left half of the dorsomesogastrium, and that sometimes this touches the genital ridge attached to the adjacent Wolffian body, just to the left. When the Wolffian body descends, and particularly when the gonad descends, it may thus carry down with it a bit of spleen. That is the reason why the spleen is sometimes found within the

tunica vaginalis or attached to the ovary. In fact, there are reports which show a strand of splenic tissue extending from the major spleen down along the left posterior gutter.

Because of these facts we opened the posterior gutter in this third patient and found a 2 cm. accessory spleen retroperitoneally, behind the lower pole of the left kidney. The fourth patient, a girl with recurrence of thrombocytopenic purpura, was explored and no accessory spleen was found. However, we found a remarkable enlargement of the mesenteric lymph nodes, together with enlargement of the retroperitoneal and celiac nodes.

In the fifth case we had a similar experience. In the sixth, a patient with congenital homolytic icterus, we were also unable to find an accessory spleen. However, the liver presented the color usually characteristic of the spleen. Biopsy of the left lobe of the liver revealed a remarkable reticuloendotheliosis involving particularly the von Kupffer cells, some of which could be shown to be phagocytic. There was also in this patient a moderate lymphadenosis.

In the seventh patient, operated upon by one of my associates, there was recurrence of thrombocytopenic purpura and a small accessory spleen was found along the greater curvature of the stomach. In the eighth and last, recurrence of congenital hemolytic icterus, it was possible for my colleague, Dean Charles A. Doan, to demonstrate radiographically the accessory spleen by the use of thorium. This was found just above the upper pole of the left kidney. It was removed recently and we are not yet certain of the end result.

Thus in eight patients with recurrence we have found in five instances an accessory spleen, in three a lymphadenosis with reticuloendotheliosis and in one an associated hyperplasia of the von Kupffer cells of the liver.

Dr. Lahey remarked about the end results of splenectomy for idiopathic neutropenia. I removed the spleen in the first case recorded in October, 1939 (Ann. Int. Med., Vol. 16, p. 1097, June, 1942). This patient was hospitalized last summer for removal of a pilonidal cyst, and careful studies were made. So far as we could determine there was no residual hematologic disturbance. Her neutrophiles had remained normal since the splenectomy.

Dr. Owen H. Wangensteen, Minneapolis: I wish to speak on a technical point. Dr. Lahey has been an exponent of removal of the spleen in total gastrectomy. Over a perior of several years, I have been aware of the circumstance that a dry wound does not regularly accompany total gastrectomy. The reason for fluid collections in the vicinity of the esophagojejunal anastomosis was not apparent; but because of this occurrence over a period of approximately two years, I have been putting in an air-vent suction of the sump or Chaffin variety down to the splenic bed after excision of the spleen and establishment of the esophagojejunal anastomosis. In a number of instances, considerable fluid has drained away—as much as 200 to 500 cc. per day, and occasionally even more; as much as 800 cc. drainage of fluid through such an air vent suction drain has been recorded in a single day. Drainage of this amount of fluid is not observed ordinarily until several days (5 to 8) have elapsed since the total gastrectomy and splenectomy were done.

A year ago, one of my associates, Dr. Ivan Baronofsky, made an unusual and startling observation concerning the nature of such fluid drainage following such operative procedure. It occurred to him that this fluid might be pancreatic juice—and such it proved to be; in any case the fluid contained as much amylase as pure pancreatic juice.

Large mortalities have been recorded attending the operation of total gastrectomy. The maintenance of a dry wound is an important item in the healing of any wound. And as surgeons are aware, the accumulation of fluid about a gastro-intestinal anastomosis does invite a subphrenic abscess; moreover, a subphrenic abscess is a more

serious situation in the presence of a gastro-intestinal suture line, in that the abscess may erode the suture line and invite fistula. Routine placement of an air vent suction drain down to the plenic bed behind the esophagojejunal anastomosis, together with employment of the jejunal wall as a posterior buttress for the posterior wall of the esophagus — these two measures have made it possible in our clinic to perform total gastrectomy with a risk which is not far out of line with that of partial gastric resection for cancer.

Such drainage of pancreatic fluid has been observed following excision of large spleens without other coincidental operative procedures. In other words, splenectomy may be accompanied by a temporary pancreatic fistual. Moreover, the febrile episodes observed occasionally after splenectomy may have their origin in such an explanation.

There are two possibilities to account for their occurrence: (1) Injury to the blood supply of the tail of the pancreas in the ligature of the splenic vessels; (2) Pancreatic ducts may actually terminate occasionally in the hilum of the spleen. Dr. Baronofsky is studying the problem at the present time. In any case, external drainage of pancreatic fluid attending splenectomy alone or splenectomy and total gastrectomy, has been observed several times in this clinic—an occurrence which suggests that an air vent suction drain probably should be employed regularly in splenectomy.

Dr. John W. Norcross, Boston (closing): I should like to emphasize what Dr. Lahey has already said concerning the excellent opportunity for co-operation between surgeon and physician in the handling of patients with splenomegaly. After careful medical study, the internist can usually establish the hematologic diagnosis.

Operative risk is often difficult to evaluate, particularly in cases of congestive splenomegaly. In this important group, if the patient can be successfully carried through the procedure and the immediate postoperative stage, he will usually derive definite benefit from the operation. In this condition, removal of the spleen will decrease the volume of blood entering the portal circuit by from 25 to 40 per cent and, accordingly, will decrease the danger of hemorrhage from engorged varices. Splenectomy will also abolish the hypersplenic effect on the bone marrow in these cases when it is present.

Careful management of the postoperative course is particularly important in this group of patients with congestive splenomegaly. The danger of infection is great, but with our present antibiotics we are in much better position than formerly to control this danger effectively. Hemorrhage of the type that comes from severe damage to liver function and which is related to the inability of the failing liver to manufacture prothrombin, can be controlled only by multiple fresh blood transfusions. The careful use of modern anticoagulants, heparin and dicoumarol, makes it possible to control impending thrombosis in the portal system in cases in which the platelet count rises to extremely high figures after splenectomy.

If we are to treat patients with splenomegaly most effectively, it is essential that such cases be recognized early, and careful palpation for an enlarged spleen should be a part of every physical examination. When patients with splenomegaly of undetermined etiology have been studied carefully over a period of several months, and if the contraindications can be ruled out definitely, splenectomy is justified.

I should like to stress the contraindications to splenectomy. First and foremost of these is the splenomegaly of agnogenic myeloid metaplasia. In this condition the spleen has taken up the function of forming the elements of the peripheral blood which are normally made in the bone marrow. Under such circumstances it is dangerous and often fatal to remove the spleen because this organ is the main source of blood cell formation. In the splenomegaly of chronic infectious conditions, only on very rare occasions should splenectomy be carried out. In general, patients with malignant conditions involving the spleen should not be subjected to splenectomy. Enlarged spleens in cases of polycythemia should not be removed.

THE TREATMENT OF RENAL INSUFFICIENCY IN THE SURGICAL PATIENT*

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ANY PLAN OF THERAPY for the patient with acute renal insufficiency of the lower nephron type should be directed at maintaining survival of the patient until such a time that adequate recovery of renal function ensues. This time interval is undoubtedly related to the degree of renal tubular and interstitial pathology present subsequent to the initial injury. In the clinical experience of the authors, this interval has varied between seven and 14 days. It may be shorter or longer since it will be modified by other factors present. (Table I.)

Several methods of internal or external hematodialysis have been suggested as a substitute for renal function during the period of renal insufficiency. (Peritoneal lavage, artificial kidney, gastro-intestinal lavage.) The main objections to such methods usually revolve around: (1) the technical difficulties involved, (2) the complications produced, or, (3) the inability of any particular method adequately to substitute for renal function. The authors have had no experience with internal or external hematodialysis.

A simple conservative plan of management which has proven successful in the last several cases of acute renal insufficiency at the University Hospital is presented. It requires no particular technical equipment and entails only a minimum of laboratory aid. The plan of management is based entirely upon the time interval required for renal tubular healing to occur following injury, and upon the premise that the patient may be maintained in a satisfactory clinical condition during this period by very conservative measures.

It has been adequately demonstrated that serious degrees of renal failure may develop following transfusion reactions, shock or prolonged hypotension, burns, various types of injuries, and from numerous other causes. The subsequent morbidity and mortality in such patients have been high in spite of the use of various forms of therapy.

Malloy[1], Lucké[2], and others, on the basis of material obtained at autopsy from known cases of renal failure following injury, transfusion reaction, etc., have pointed out that the significant pathologic changes in the renal parenchyma, while not necessarily specific, are practically constant in location. These lesions are for the most part confined primarily to the distal tubular segments of the nephron units. They are often reversible in that healing of the areas

* Read before the American Surgical Association, Quebec City, Quebec, May 27, 1948.

of tubular damage may ensue with recovery of adequate renal function and survival of the patient.

Muirhead, et al[3], have pointed out that the poor past record in the management of these cases may be attributed to one of two general causes: (1) the injury sustained by the patient is so great as to preclude the success of any type of management or, (2) the type of management in the past has not been conducive to the proper recovery of these cases. (The primary disease present in the patient, such as a far advanced carcinoma of the stomach with perforation, may preclude ultimate recovery from the primary disease, but does not necessarily prevent the recovery from renal failure which may have developed in such a patient). Cases 6 and 10 are examples of these situations.

TABLE I.—*Electrolyte Excretion Preceding and During the Phase of Diuresis.*

Patient	Day	Urine Volume cc.	—Urine*— Na	Cl	—Serum*— Na	Cl	Plasma Electrolyte Volume or 0.9% NaCl Equivalent**
Case 2	11-12-13	5325	90.8	78.0	120	87	49.8 Gm. NaCl — 5.53 liters of 0.9% NaCl in 9.4 liters urine. Equivalent to 6.8 liters E.C.F. on the basis of Cl, or 5.86 liters on the basis of Na.
	14	4100	89.7	73.0	...	...	
Case 1	9	240	...	42.3	139.7	98.5	0.097 liters — 0.4 Gm. NaCl.
	14	2000	...	46.0	133.7	93.3	0.876 liters — 5.38 Gm. NaCl.
	20	8075	...	73.2	135.4	98.2	34.6 Gm. NaCl — 3844 cc. 0.9% NaCl or 5.63 liters E.C.F. equivalent.
Case 4	15	3200	90.2	...	...	...	16.88 Gm. NaCl — 1875 cc. 0.9% NaCl or 1.99 liters E.C.F. on basis of Na.

* M. Eq/L.

** Estimated on the basis of Na — 145 M. eq./liter E.C.F. and Cl — 105 M. eq./L. E.C.F.

Renal tubular epithelium which has been the site of injury may heal within a relatively brief period of time. Evidences of such healing have been observed in autopsy material in our own series of cases as early as the 8th day. Clinically, recovery of the ability of the kidney to excrete urine has usually occurred in our own experience within seven to 14 days. It has been assumed that this onset of diuresis reflects progress in healing of the renal parenchymal lesion.

THE MANAGEMENT OF ACUTE RENAL INSUFFICIENCY*

The plan of therapy falls into three phases, (1) the period of shock, hemolysis, injury, etc., (2) the period of renal insufficiency lasting one to 14 days, and (3) the period of recovery diuresis which ordinarily lasts five to seven days. The actual treatment varies considerably during these three phases. During the period of shock or hypotension, treatment consists of the measures usually employed, i.e. blood transfusions, oxygen, intravenous fluids,

* Excluding internal or external hematodialysis. This three-phase plan is similar to that suggested by Muirhead.[3]

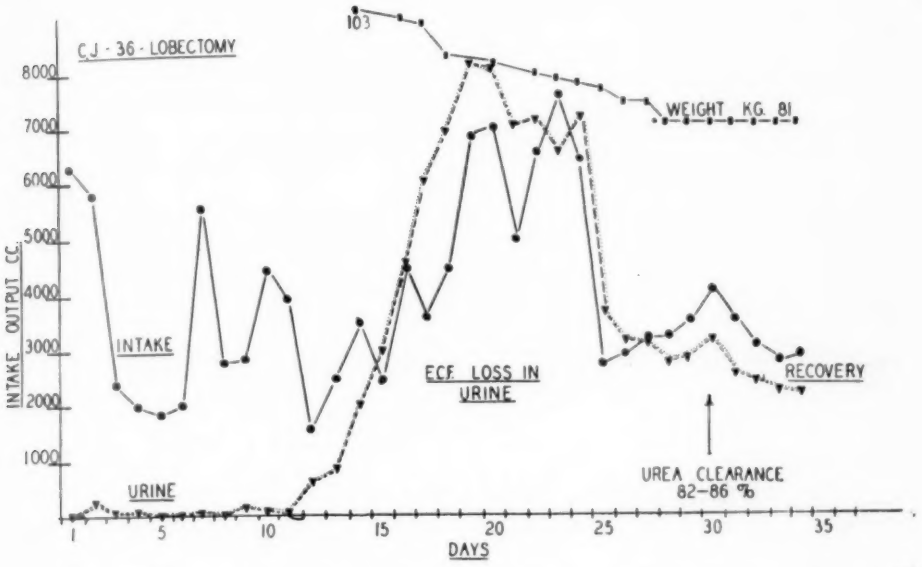

FIG. 1 (Case 1).—The oliguria-diuresis curve in a patient with renal insufficiency initiated by prolonged hypotension. The CO_2 combining power was maintained at satisfactory levels. Patient alive and well one year later.

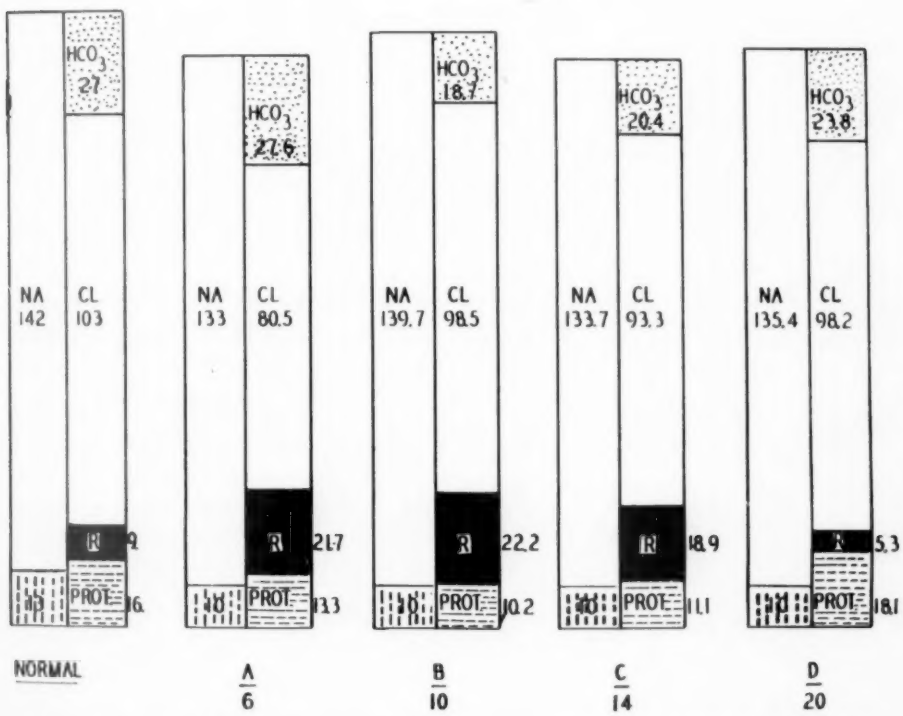

FIG. 2 (Case 1).—Chemical analyses of the blood at various intervals during the period of renal insufficiency and during recovery.

TABLE II.—*Initiating and Perpetuating Factors in 10 Cases of Lower Nephron Nephrosis.*

Case	Termination	Recovery Renal Function	Transfusion Reaction	Initiating and Perpetuating Factors Present: Shock or Hypotension	Inflammation or Infection	Injury or Operation	Previous Renal Damage	Sulfa Therapy
1	Recovery	+	?	Moderate	Small Empyema	Lobectomy	—	—
2	Recovery	+	+	Mild	—	Gastrectomy	?	—
3	Recovery	+	+	Moderate	Wound	Cystectomy Hemorrhage	Hydronephrosis	?
4	Fatal	+	?	Severe	—	Splanchnicectomy	Moderate	—
5	Recovery	+	—	—	—	—	Hydronephrosis	+
6	Fatal	—	+	Mild	—	Fracture	—	++
7	Fatal	—	—	Mild	Liver Abscess	Choledocho-Duodenostomy	Arteriosclerosis	+
8	Fatal	Partial	—	Severe	Pyothorax	Esophago-Gastrectomy	Aplastic Left Kidney	Intensive
9	Fatal	—	—	Moderate	Gas Gangrene	Amputation	—	+
10	Fatal	+	+	—	Perforation Ca Stomach	—	Arteriosclerosis	—

Cases 1-5 and 10 were treated by the three-phase plan of management described in this article. Cases 6-9 were random selections of patients from the various surgical services prior to the introduction of this plan of therapy where autopsy material was available.

etc. As soon as renal insufficiency becomes manifest, a sample of blood from the patient is sent to the blood bank for re-checking of the original cross match, if this is thought to be the source of the difficulty, extra-renal parenchymal urinary tract obstruction is excluded to the satisfaction of the attending staff, and the total fluid intake of the patient is immediately limited to the daily calculated insensible loss, (perspiration and respiration). This will vary between 1000 and 1800 cc. in the afebrile patient and consists of water given orally or 5% glucose in distilled water intravenously. This restriction of total fluid intake is enforced until adequate urine output ensues.

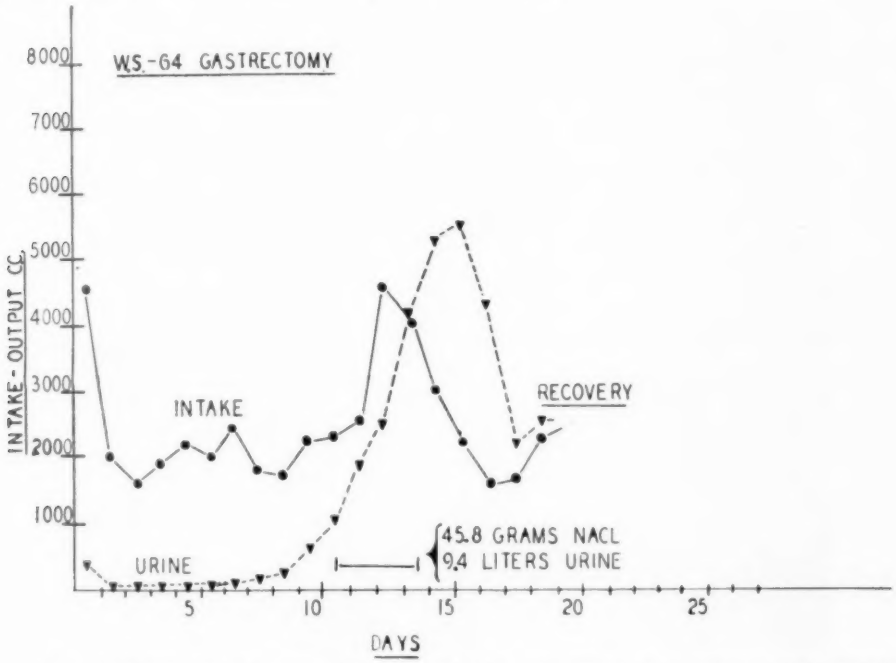

FIG. 3 (Case 2).—Characteristic oliguria-diuresis curve in a patient with anuria following a hemolytic transfusion reaction. Subtotal gastrectomy for carcinoma. Recovery. Note the declination of intake and the increment of urine output during the phase of recovery diuresis.

Periodic blood NPN and carbon-dioxide combining power determinations are made throughout the period of renal insufficiency. Such determinations are optional but at the same time desirable. Correction of the CO_2 combining power is carried out only when levels of 40 volumes % or lower are reached. This is achieved by the use of sodium bicarbonate orally or sodium lactate (one-sixth molar) intravenously. Such measures modify the CO_2 combining power without necessarily correcting the actual cause of the acidosis. It should be recognized that the use of these solutions leads to the introduction of sodium salts in the presence of renal insufficiency.

Calcium gluconate or levulinate intravenously in 10 cc. doses is employed daily throughout the period of renal insufficiency to allay the development of

the signs and symptoms of tetany. This measure is also optional. The diet given these patients has varied considerably and the authors have noted no untoward effects from either high protein intake or restriction. The salt content of the diet should be restricted to 200-800 mg/day until diuresis occurs. If a positive fluid load, i.e. endema, has occurred either during or prior to treatment, rigid restriction of salt and fluid intake is employed until the positive fluid load is corrected.

During the third phase of treatment (recovery diuresis) an interesting paradox may occur. Recovery of renal function is made apparent by the

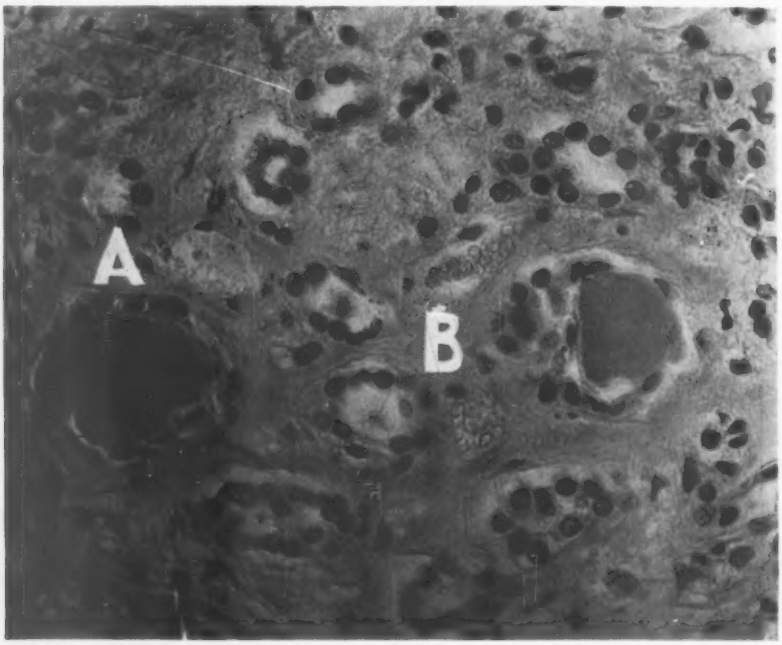

FIG. 4 (Case 10).—Hyaline casts in the tubules of the medulla. The pyknosis of the nuclei (A,B) are indicative of regeneration of epithelium in a patient with a perforated carcinoma of the stomach who died 14 days following a transfusion reaction. Recovery diuresis present at the time of death.

daily increase in urine output. (Figs. 1, 2, 3). At the same time, abnormal water and electrolyte losses in this urine may place the life of the patient in jeopardy from acute dehydration or hypopotassemia (Table II). Therapy at this time is therefore directed at accurate replacement of urinary losses of sodium, potassium[3], and water. This is mandatory if acute dehydration is to be prevented. Urine analyses for sodium, potassium and chloride at this time are desirable. The method of replacement of salt and water losses during this period has been achieved through the use of Ringer's Solution intravenously and/or a 0.5% salt solution orally.* Inasmuch as it is extremely difficult to

* NaCl—4.0 Gm./liter plus $NaHCO_3$ 1.0 Gm./liter.

either anticipate or replace a urine output of eight or nine liters in 24 hours, careful attention is given to the daily increment in urine output once the phase of recovery diuresis has become manifest. When the urine output reaches a level of 5 liters or more daily, an equivalent amount of Ringer's solution intravenously is given. Any difference between output and intake is paralleled by an oral intake of salt solution equivalent to the amount of urine passed with each urination. Decreasing the fluid intake has not reduced the increment in urine output even when such a plan has been carried out over a four

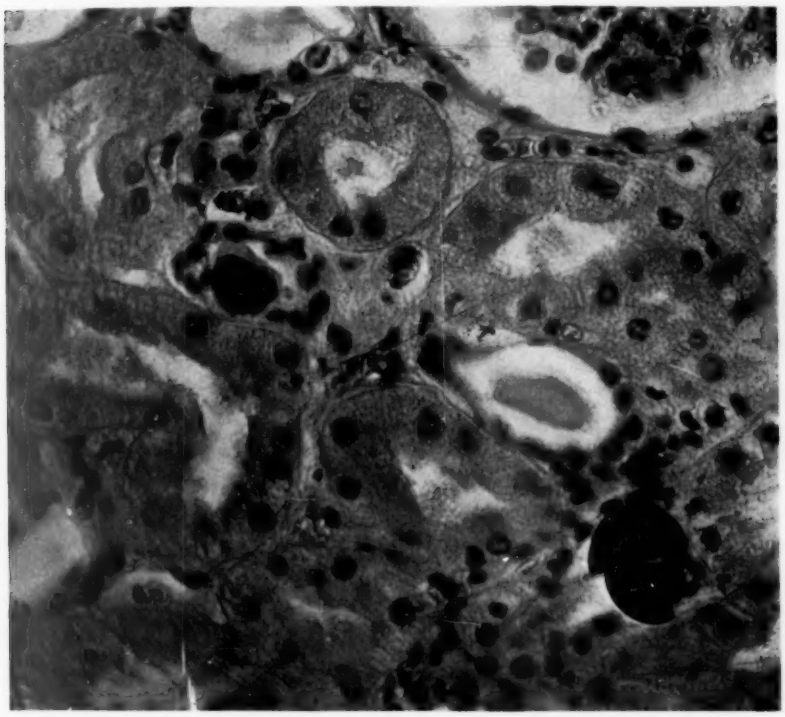

FIG. 5 (Case 10).—Crystals in the distal convoluted tubules. Cloudy swelling of epithelium in the proximal convoluted tubules with precipitated protein in the lumen.

day period. (Fig. 3). The degree of recovery diuresis will vary tremendously with different patients, in some instances being quite marked, in others, of little consequence.

Following restitution of the urine output to normal levels, renal function tests are carried out. These tests are optional, but do reflect the degree of recovery which has taken place. The blood NPN has not returned to normal levels, in the experience of the authors, for some 28-35 days after the initiation of renal insufficiency. Muirhead[3] has pointed out the inability of the kidneys under these circumstances adequately to excrete nitrogenous waste

materials despite a recovery diuresis. In cases 1, 2, 3, 4, the blood NPN reached a peak increment and then a descent to lower values between the 12th and 14th day in each case. Weight loss during the period of diuresis has been quite striking in two of the patients in the recovery group (Cases I, II).

CASE HISTORIES

Patients 1, 2, 3, 4, 5 and 10 were treated by the three phase plan of management. Patients 6, 7, 8, and 9 represented previous fatalities on the

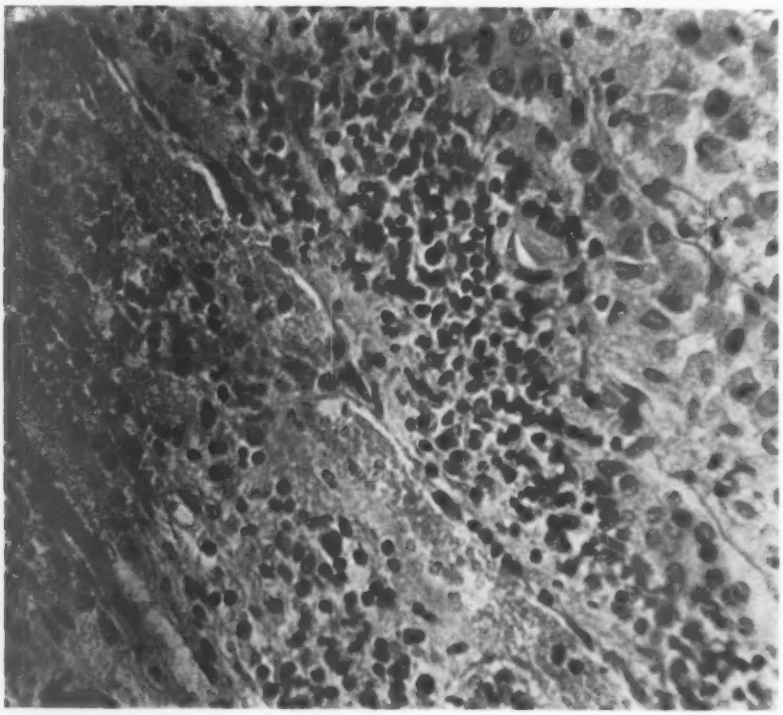

FIG. 6 (Case 8).—Dilated vasa recti with dense perivascular infiltrations indicative of sulfonamide hypersensitivity in the right kidney occurring in a patient in whom renal insufficiency was initiated by shock. Aplastic left kidney. Death 9 days following partial esophagogastrectomy for carcinoma.

surgical service and were selected for the availability of autopsy material and because the therapy which they had received for their renal insufficiency was in direct contrast to the management now advised.

Case 1.—C. J., age 36. Bronchiectases of the left lower lobe and lingula. Left lower lobectomy and lingulectomy 3/10/47. Prolonged hypotension despite repeated transfusions of whole blood (3000 cc.). No untoward reaction to the transfusion was noted. The urine output in cubic centimeters on successive days was 0, 230, 60, 60, 0, 0, 30, 15, 240, 160, 120, 647, 807, 1043, 2000, 3000, 4500, 6200, 6925, 8115, 8075, 7000, 7200, 6656, 7200, 3700, 3275, 3125, etc. (See Figs. 1, 2, and Table II.) During the entire course of his illness the patient was alert and cooperative. Subsequent hypoproteinemia and anemia were corrected with

concentrated serum albumin I.V. and transfusions of washed red cells and dietary measures. Vigorous replacement of salt losses during the period of diuresis was carried out. Despite a considerable weight loss, the patient recovered from the renal insufficiency (14 days) uneventfully and was discharged from the hospital feeling very well. Patient alive and well 1 year later.

Case 2.—W. S., age 64. Carcinoma of the stomach. Subtotal gastrectomy 2/6/48. Transfusion reaction with hemolytic jaundice, anuria (Fig. 3, Table II.) The patient received three transfusions during and following operation. Re-check of the original cross-match revealed no errors, both the recipient and 3 donors being typed A Rh =.

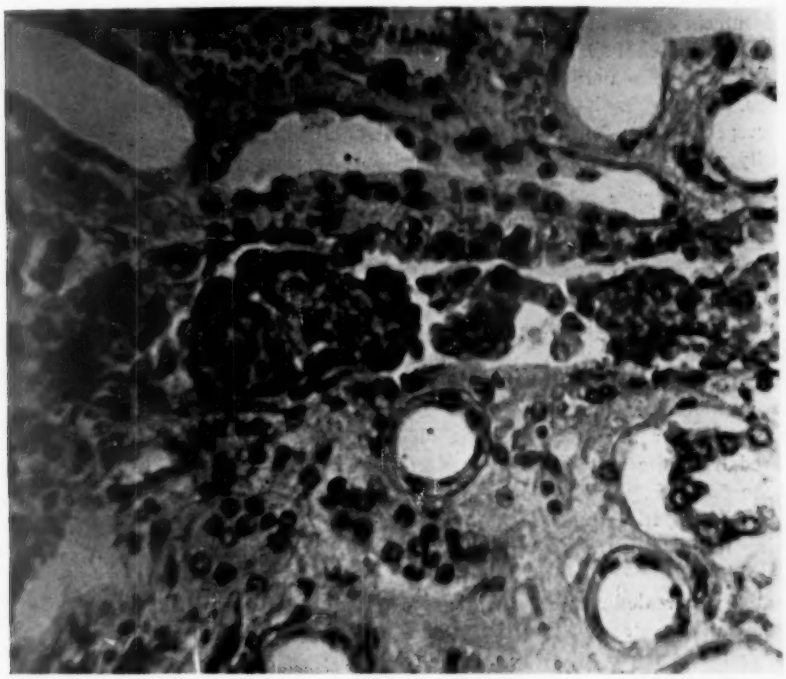

FIG. 7 (Case 6).—Granular heme casts in the distal portion of the nephron in a case of hemolytic transfusion reaction.

It was felt that the patient had been previously sensitized to a peculiar sub-group in the third donor. His history revealed that he had received both blood and plasma elsewhere. The first voided urine sample (P.O.) was port-wine in color and positive to both benzidine and guaiac. Urine output in cc.'s on successive days was 420, 16, 34, 50, 35, 52, 70, 160, 256, 705, 1065, 1815, 2445, 4100, 5200, 5325, 4250, 2150, etc. The patient remained alert, ambulatory and cooperative during the period of renal insufficiency (10 days) and recovered uneventfully.

Case 3.—E. H., age 64. Carcinoma of the urinary bladder. Cystectomy and bilateral uretero-sigmoidostomy 7/20/47. Hemolytic transfusion reaction with jaundice. Anuria. Hypertension and mild right hydronephrosis.

The patient was placed on a program of daily replacement of insensible loss of fluid —calculated at 1500 cc., periodic correction of the CO_2 combining power, calcium salts, 1 gram daily I.V., and replacement of salt loss. The urine output on successive days was 0, 0, 125, 75, 350, 450, 514, 655, 1470, etc. The blood NPN rose steadily to 296 mg.%

14 days after operation. The patient remained alert and cooperative during his entire illness and underwent a satisfactory recovery. Alive and well 4 months later. (See Table I.)

Case 4.—C. C., age 54. Essential hypertension. Bilateral splanchnicectomy and dorsal sympathectomy 1/8/48. Severe hypotension P.O. Anuria.

The patient's blood pressure fell to low levels in the immediate postoperative period and returned to normal only after vigorous supportive therapy. The urine output on successive days was 130, 150, 150, 850, 700, 710, 700, 1500, 1700, 2250, 2900, 2885, 2100, 3990, 3200, 2900, 2900, etc. During his entire illness the patient remained in a semi-stupor with periodic muscular twitchings which did not respond to any of various forms of therapy employed. These changes were believed to represent cerebral damage. Recovery from renal insuffiency began on the 8th P.O. day and it was felt that recovery would take place. On the 20th P.O. day, the patient experienced an episode of diarrhea with acute circulatory collapse and dehydration. This responded to parenteral therapy with salt solutions. Two days later, the patient expired from sudden cardiac decompensation. In retrospect, the possibility of hypopotassemia and insufficient salt replacement undoubtedly played a role in the sudden demise (Table II).

Case 5.—V.G., age 42. Carcinoma of the cervix grade IV-B with osseous metastases. Previous intensive irradiation therapy. Left nephrectomy, 1942, for calculous disease. Right hydronephrosis. Anuria from presumed sulfonamide sensitivity. Severe anemia.

For 24 hours prior to admission (2/28/48) the patient had been anuric. This was presumed to be due to ureteral obstruction. Cystoscopy and ureteral catheterization revealed an absence of urine both in the bladder and in the renal pelvis. Urine output on successive days was 0, 24, 275, 55, 50, 80, 1270, 1250, 1050, 1600, 1800, etc. In view of the positive fluid load on admission, fluid intake was restricted to an average of 1000 cc. daily for the first five days. The patient remained alert and cooperative and recovered from the renal insufficiency on a very conservative program.

Case 6.—F.S., age 41. Commenuted supracondylar fracture left humerus. Anuria following incompatible blood transfusion. (Donor A+, recipient 0+.) Death nine days following transfusion reaction. Total intake 31,545 cc., total urine output 730 cc. during this period.

Autopsy revealed acute hemorrhagic parenchymatous nephritis (Fig. 7), multiple infarcts, emboli, petecheal hemorrhages, intense pulmonary congestion and edema. Bilateral hydrothorax.

Case 7.—G. H., age 61. Chronic cholecystitis with lithiasis. Common duct stone. Obstructive jaundice. Liver abscess. Choledochoduodenostomy 4/15/43. Progressive renal insufficiency P.O. History of anuria in family from similar operation. Death six days P.O. Total intake 33,375 cc. Total urine output 1734 cc.

Autopsy revealed active ascending cholangitis, liver abscesses, bilateral hydrothorax, ascites, arteriosclerotic nephropathy and lower nephron nephrosis.

Case 8.—B.G., age 62. Adenocarcinoma cardia of the stomach with esophageal extension. Transthoracic esophago-gastrectomy 6/8/42. Prolonged P.O. hypotension (12 hours). Death 8 days following resection.

The patient received a total fluid intake of 38,835 cc. in the P.O. period. Total urine output, 9,130 cc.

Autopsy revealed an aplasia of the left kidney and lower nephron nephrosis of the right kidney (Fig. 6). (Sulfonamides had been administered in the P.O. period.) Pulmonary edema and atelectasis. Advanced arterio-sclerotic nephropathy.

Case 9.—R.V., age 30. Gas gangrene left leg. Amputation five days prior to admission. Disarticulation at knee and debridement of thigh 3/12/43. Death 3/16/43.

The patient was in deep shock on admission and remained moribund during his course in the hospital. Total intake (3 days) 12,175 cc. Urine output 665 cc.

Autopsy revealed lower nephron nephrosis and pulmonary edema with bilateral hydrothorax. Sulfa crystals were present in the renal tubules.

Case 10.—H.S., age 63. Far advanced carcinoma of the stomach with perforation and localized peritonitis. Multiple transfusion reactions (hyperthermia) and anuria. Gradual recovery renal function with urine output reaching 2600 cc. on 13th day. During this period patient was moribund from primary disease. Autopsy revealed lower nephron nephrosis (Fig. 4, 5) with advanced healing of tubular epithelium and crystals of undetermined etiology. Carcinoma of the stomach with perforation.

SUMMARY

A simple program of treatment for acute renal insufficiency of the lower nephron type is presented. The clinical course of the patients so treated has been entirely satisfactory.

It is conceivable that should renal tubular function fail to recover in the expected time interval, more energetic measures including hematodialysis should be employed. The authors have not found this necessary in the series of cases which they have treated.

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The authors wish to express their appreciation to Dr. A. J. French of the Department of Pathology, University of Michigan Medical School, for helpful assistance.

DISCUSSION:—DR. E. I. EVANS, Richmond, Va.: I am very sorry that because of the time limit Dr. Campbell did not get to present his complete material. We have learned from his and other work that one simply must not force the kidney to do work that it cannot do. In other words, we must let nature do what nature can do and, if nature cannot repair the damage, there is not much that one can do about tubular degeneration.

I rise only to point out that there is a preventive aspect in this, which I am sure he would have brought out had he had time. From all the work done on clinical shock during the past five or six years one thing has been learned, namely, if one is to prevent the shock kidney, one must keep to a very short period, the time the patient is in actual shock. One cannot take a long time to get infusions begun, one cannot expect good results in the therapy of shock when insufficient amounts of blood are given, and so on. There is a safe period of only about two or three hours at the most and if shock is prolonged beyond this period, tubular regeneration of the kidney cannot take place. We should not forget the important preventive aspect of this in considering the shock kidney.

DR. FREDERICK A. COLLER, Ann Arbor (closing): Dr. Campbell has given you briefly a picture of the work of Trueta and his associates, Lucke, Mallory and others,

which I will not amplify except to express our indebtedness also to Muirhead and Hill. He has not had time to present to you in any detail the treatment of these patients with anuria associated with hypotension, tissue damage or blood incompatibilities. I will give an outline of the management of the two cases he has mentioned and shown on slides.

It can be divided into four phases: Phase I, in which the patient is or may be in hypotension. We agree with Dr. Evans that this should be corrected as soon as possible, otherwise the state may become irreversible. Transfusion of properly chosen blood is usually necessary. Phase II is that of obliguria or anuria. We have learned, as have others, that forcing fluid in the endeavor to force the kidney to work nearly always ends in disaster. Therefore, the patient is given only the amount of water that he is losing from his skin and lungs, which at comfortable environmental temperature is usually 1200 to 1500 cc. a day. This is given orally when possible, otherwise parenterally as 5 per cent glucose in water. The CO_2 combining power should be followed daily and if it falls below 40, the impending acidosis must be corrected by the administration of sodium bicarbonate by mouth or sodium lactate solution intravenously. The patient is allowed to eat if he will do so; any light diet with low proteins seems satisfactory. If muscular twitchings develop, it will be found that the utilizable calcium is diminished, probably combining with phosphates, sulfates or bile salts in case of jaundice, and one gram of calcium glucosate is given each day. This program is carried out until diuresis occurs, which may not be for two or more weeks. The patients are comfortable and conscious if acidosis is not allowed to supervene in spite of the rising N.P.N. The third phase of the management covers the phase of diuresis. This must be watched for since it may come suddenly with the passage of several liters of urine. The water and salt must be replaced accurately and as lost. If this is not done, dehydration may cause death. Interestingly enough, the urine passed at this time is not concentrated, 1.010 to 1.014. The phase of diuresis may last two or three or more days, when the patient's condition improves and the urinary output approximates normal. The kidney does not return immediately to normal and we pass to Phase IV, in which the kidney recovers its former function, which may take a month or more. No special therapy is indicated. The high blood N.P.N. slowly declines. We feel that no special effort should be made to influence this chemical finding since other chemical abnormalities are more important.

We feel that not only should these patients be kept on the dry side, but that all patients who have had extensive traumatic operations, especially those that last many hours often associated with blood loss and hypotension, should also be given water with caution. The phrase "force fluids" should be abolished. It is nearly routine practice to start fluids with the operation and keep it flowing throughout the entire time of operation. The longer the operation the greater will be the trauma and the greater the chance for renal damage. The amount of fluid given should not be determined by the length of the operation, but upon other criteria. We have recently studied the management of water in patients undergoing combined abdominoperineal resection and in every instance there has been an adequate output of urine for 36 hours; that is, there has been water retention. The urine in this phase has the same characteristics as that passed by the post-anuric patient in the diuretic phase. Patients suffering from trauma, operative or otherwise, should be given fluids with great care. If water is given that cannot be utilized or excreted, harm may be done.

THE SIGNIFICANCE OF URINE CHLORIDE DETERMINATION IN THE DETECTION AND TREATMENT OF DEHYDRATION WITH SALT DEPLETION*

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WITH THE TECHNICAL ASSISTANCE OF

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FROM THE SURGICAL RESEARCH LABORATORY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA.
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THE PHYSICIAN FREQUENTLY faces the problem of how much and what kind of parenteral fluids to administer; in most cases the problem is the quantitative one of how much water and how much salt the patient needs. Neither physical examination nor estimation of plasma chloride concentration gives adequate information. However, our experiments with dehydrated human subjects indicate that, when renal or adrenal function is not damageed, the problem can be solved by measuring the urine volume excretion and urine chloride concentration, both of which are bedside determinations.*

The physiologic principles of water and electrolyte balances, which have been developed especially by the work of Gamble[2] and Peters,[3] are well reviewed by Mariott.[4] Body water may be regarded as separated into three compartments: plasma, interstitial tissue fluid, and intracellular fluid (Fig. 1). Body electrolytes may be regarded as separated into two compartments: intracellular and extracellular, the latter corresponding to the plasma plus interstitial spaces (Fig. 2). Roughly speaking, the capillary membrane is freely permeable to water and electrolytes while the cell membrane is freely permeable to water alone. Equality of osmotic pressure throughout the body fluids, intra- and extracellular, is maintained by water shifts across all membranes and electrolyte shifts across the capillary membrane. The shifting extracellular electrolyte is predominantly sodium chloride (Fig. 2). Under ordinary conditions, the kidneys adjust excretion of water, and sodium chloride and other solids so accurately to intake that the volume and electrolyte concentration of the extracellular fluid are kept extraordinarily constant, providing the cells with the "internal environment" of Claude Bernard. For the cells to function normally, the volume of extracellular fluid must be kept adequate, and the

* By the method of Fantus,[1] urine chloride concentration can be quickly measured at the bedside with an accuracy of plus or minus 0.5 grams NaCl per liter of urine. The necessary apparatus and solutions are: a test tube, a medicine dropper, 20% potassium chromate, 2.9% silver nitrate, and distilled water for rinsing the dropper. To 10 drops of urine in a test tube, add 1 drop of potassium chromate solution and then silver nitrate solution, a drop at a time with shaking until the test tube contents suddenly change from yellow to brick red. The same dropper must be used throughout and rinsed between solutions. The number of silver nitrate drops required to produce the color change equals the urine sodium chloride concentration in grams per liter. Tests on 50 random hospital urine samples gave an average of 7.37 Gm. NaCl per liter urine with variations from 1 to 16 Gm. per liter.

* Read before the American Surgical Association, May 27, 1948.

composition and pH must be kept within "physiological" limits; the osmotic pressure must be kept near that of 0.9% NaCl solution.

Local deviations from isotonicity are prevented by rapid water and salt shifts within the body; abnormal changes in the volume or composition of the total body fluids are prevented by the kidneys. When either water or salt intake is low or extra-renal loss is excessive, isotonicity is safeguarded by a corresponding decrease in either water or salt output by the kidneys. When renal mechanisms are normal one may expect to find small urine volumes with water depletion and low urine salt concentration and excretion with salt depletion. Such relationships are illustrated in the experiment presented below, and form the basis for the plan recommended for guiding parenteral fluid therapy.

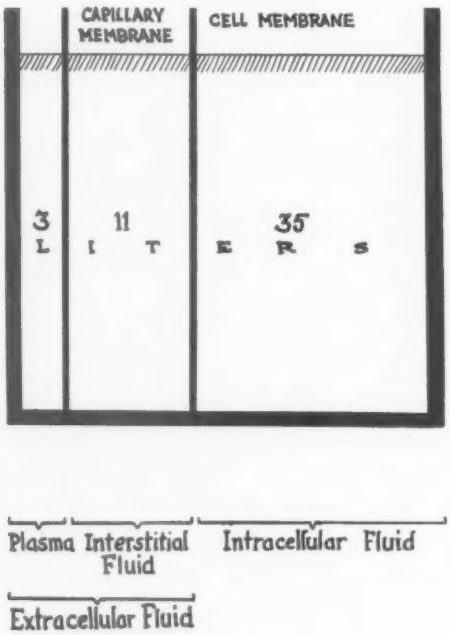

FIG. 1.—Body fluid compartments of normal 70 kg. man.

As Marriott points out,[4] dehydration is a term that covers two conditions that differ in cause, in physiologic and clinical effects, and in treatment needed. These conditions, named according to their initiating causes, are primary water depletion and primary salt depletion. (Marriott calls them "pure" depletion, but the term "pure" seems unfortunate, because salt deprivation or loss invokes accompanying water loss, and water deprivation or loss invokes salt loss.)

Primary water depletion is seen in conditions in which, usually because of generalized weakness or dysphagia, patients fail to drink adequate amounts of fluid. In debilitated patients it occurs more commonly than is recognized. The chloride concentration of the plasma may remain normal; the kidneys usually excrete enough salt to maintain extracellular isotonicity.

Primary salt depletion occurs when there is abnormal loss of salt from the body with adequate water intake. The salt loss may occur in profuse sweating, excessive vomiting, gastric suction, diarrhea or alimentary tract fistulae.* Since the kidneys will not retain water without salt until the salt loss is severe, depletion of body water occurs, even if adequate amounts of water are drunk. Thus, though total body salt may be depleted, plasma chloride concentration

* The discussions and conclusions set forth in this writing do not pertain to the unusual electrolyte maladjustments encountered in Addison's disease.

may remain relatively normal so long as the extracellular fluid volume diminishes enough to compensate for the salt loss, and water excretion may remain adequate despite diminished extracellular fluid volume.

Figures 3 and 4 (taken from Marriott) show the theoretical water redistributions between the body compartments in primary water and primary salt depletion respectively.

With *primary water depletion* (Fig. 3) the extracellular fluid tends to become *hypertonic,* but this tendency is combated by two mechanisms; water moves across the cell membrane into the extracellular space, and the kidneys diminish their water output to the minimum obtainable by tubular reabsorp-

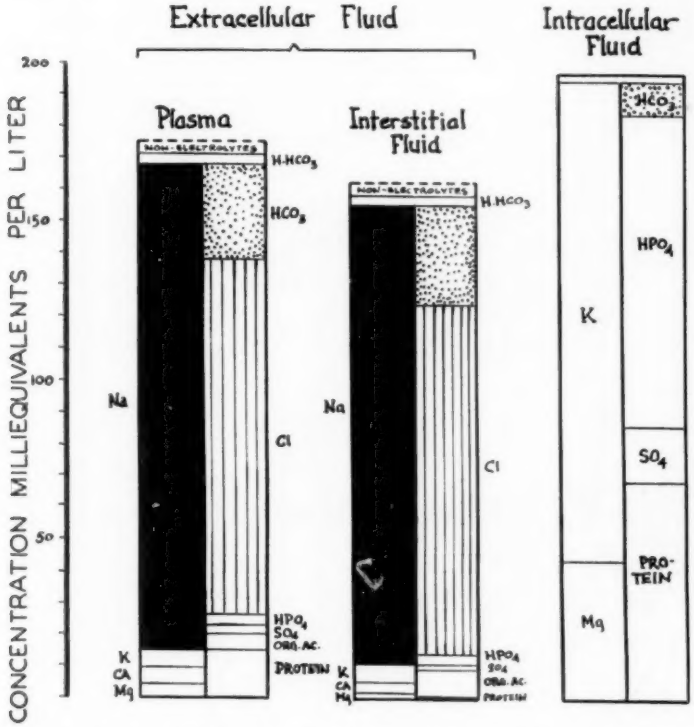

FIG. 2.—Composition of body fluid compartments of normal man.

tion. Although intracellular dehydration is marked, there may be no great change in either the plasma volume or electrolyte concentration. In this condition one may expect a *minimal urine volume,* normal or increased plasma and urine chloride concentrations, and no cardiovascular changes referable to diminished plasma volume.

With *primary salt depletion* (Fig. 4) the extracellular fluid tends to become *hypotonic.* The kidneys exert themselves to combat this tendency; *they continue to excrete water but practically no salt.* Plasma chloride concentration falls only when the kidneys can no longer excrete enough extracellular water to compensate for the salt loss. When plasma chloride con-

centration does fall, the loss of body water may be greatly out of proportion to the relative decrease in plasma chloride concentration. Shrinkage of plasma volume may become so great that clinical shock may develop.

In both primary water depletion and primary salt depletion, the kidneys exert maximum efforts to maintain isotonicity of the plasma and interstitial fluids, and in these efforts excrete urine that shows variations in volume and salt concentration greatly exceeding the variations in volume and salt concentration that occur in the plasma. The decrease of water excretion in pri-

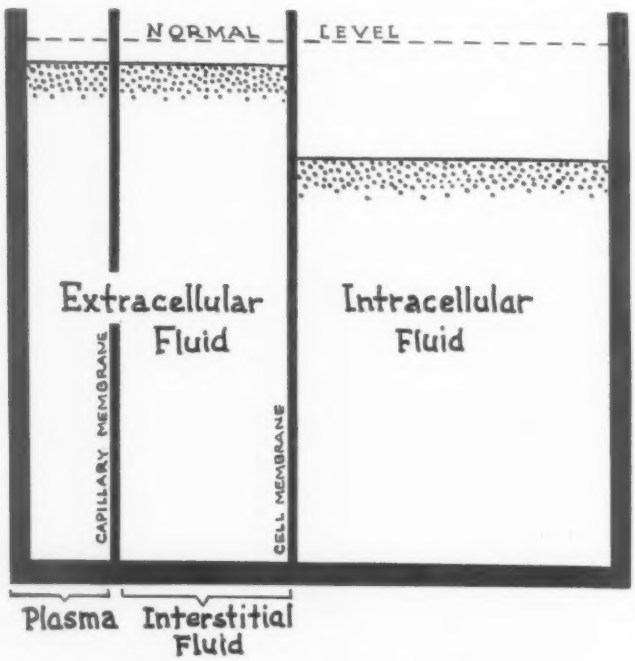

FIG. 3.—Water depletion.

mary water depletion, and of salt excretion in primary salt depletion, becomes marked when the plasma changes have hardly exceeded the normal range. Hence, it appears that, provided the kidneys are uninjured, urinary analyses can provide more sensitive indication of the occurrence and type of dehydration than can plasma analyses; that is, urine analyses can be expected to show earlier and more definitely than plasma analyses when body conditions change in either type of dehydration, from the normal to the abnormal.

On the other hand, since the kidneys respond early with nearly maximal limitation of water or salt output, it follows that urine analysis cannot be relied on to show the difference between moderate and severe dehydration of either type. The severity of the depletion may be determined either by observing the amount of water and salt therapy required to reestablish the excretion of water or salt, or by plasma measurements such as chloride and CO_2 concentration, specific gravity and blood hematocrit.

When the kidneys are diseased, or injured by shock or severe dehydration, the urine probably does not indicate internal conditions of salt and water content as accurately as when the kidneys are normal. Even kidneys which have been apparently normal one day, may, as the result of a transitory period of shock, be so damaged that the next day they excrete only a small volume of urine with little solids of any kind. This may occur in the immediate post-

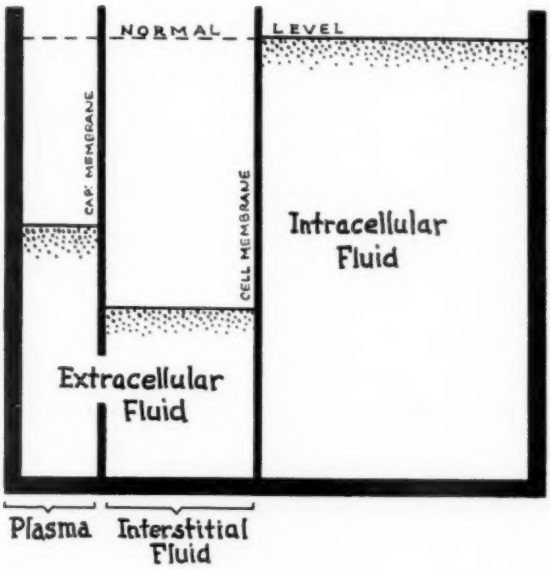

FIG. 4.—Salt depletion.

operative patient. Possibly salt retention postoperatively and during times of stress may result from the so-called "alarm reaction," a physiological state resulting from adrenal hormone secretion. Coller[5] and Moyer[6] have shown that postoperative patients tend to retain salt, and they have cautioned against overloading the patient with salt. Urine salt concentration or excretion cannot be used as a guide to salt therapy under conditions of renal salt retention. Further studies are needed to determine the conditions under which the kid-

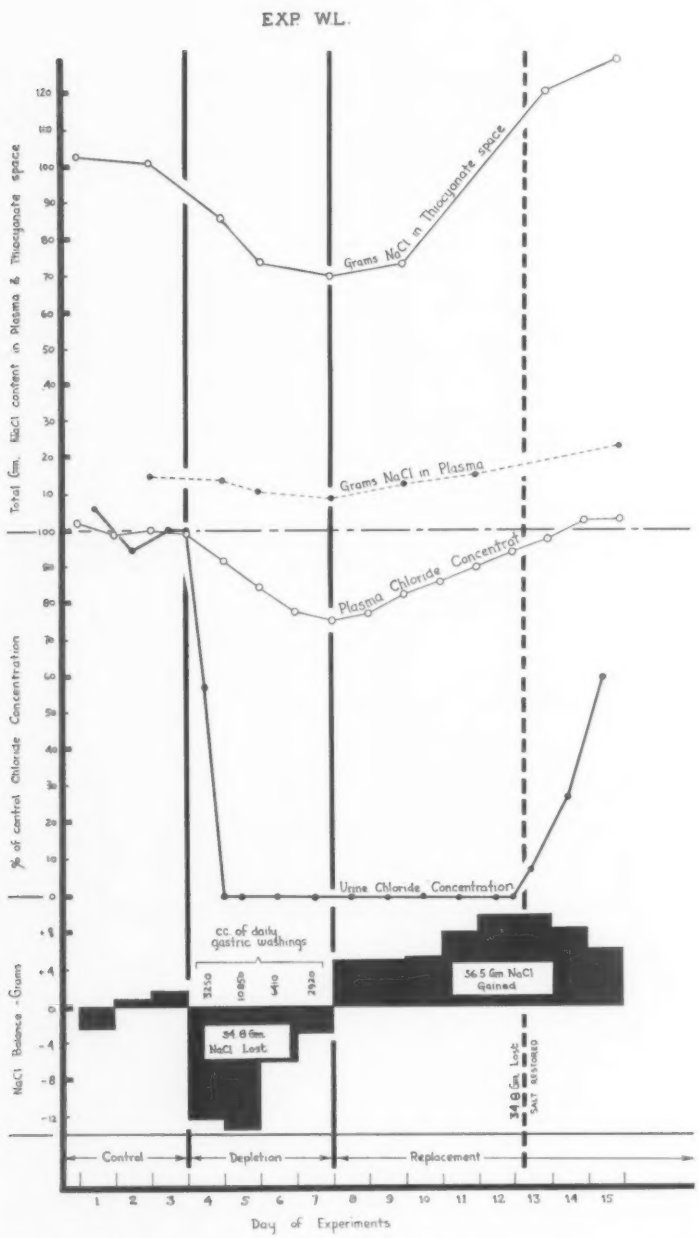

FIG. 5.—Human volunteer experimental demonstration of water and salt depletion showing (1) the renal threshold level of about 95 percent normal plasma chloride concentration, (2) the greater sensitivity of urine chloride concentration as opposed to plasma chloride concentration as an index of salt depletion and replacement, (3) the excessive water and salt retention resulting from continued saline infusions after chlorides reappear in the urine.

neys do retain salt. Further studies are also needed to rule out the possibility of salt "spillage" into the urine during and following saline infusion. Such spillage could falsely indicate adequate salt replacement.

In the great majority of cases of dehydration encountered, however, urine analysis serves well to indicate early the occurrence and type of dehydration and to indicate when therapy is necessary or has been adequate to return the volume and salt content of the plasma and interstitial fluids to their normal ranges.

EXPERIMENTAL PROCEDURE

The following experiment, which is one of three, illustrates the applicability of the above principles in a case of mixed salt and water depletion caused by prolonged gastric suction.

W. L., a healthy medical student, voluntarily subjected himself to a carefully controlled 15-day water and salt balance study. This study (Fig. 5, Tables I, II, and III) may be divided into three periods: (1) Preliminary control—the first three days. Daily measurements were made during this control period and their average taken as "control." (2) Depletion period or period of gastric suction—the next four days. Constant gastric suction during this period produced a marked mixed water and salt depletion. Water was drunk as desired but was all recovered by gastric suction. No parenteral fluids were administered. (3) Replacement period—the last eight days. Water was drunk as desired. Salt depletion was slowly overcome by a measured dietary intake (0.8 to 1.2 Gm. NaCl daily), supplemented by intravenous 0.9% saline. The salt supply of the body was replaced slowly in order to increase the number of days over which the replacement could be observed. Five hundred cc. of 0.9% saline (4.5 Gm. NaCl) solution were given daily for three days, but since complete replacement appeared unlikely within the 15 days available for the experiment, daily 0.9% saline solution administration was increased to 750 cc. on the fourth day and to 1000 cc. the last four days. The experiment was ended when plasma chloride concentration no longer increased.

All chloride determinations were done in duplicate, using the open Carius method.[7] The salt intake was measured by chloride determinations of aliquot samples of diet and infusion solutions. Salt output was determined by measuring the volume and chloride concentration of 24-hour urine and gastric suction collections.

In order to compare urine and plasma chloride concentrations on the same chart, they are plotted as "per cent of control," the "control" values being the average of the control period concentrations.

The total salt content of the plasma was measured by multiplying the plasma salt concentration (calculated from chloride) times the plasma volume, the latter being measured with T-1824 blue dye.[8] Total extracellular space salt content was estimated by multiplying the plasma salt concentration by the thiocyanate space volume.[8] Both plasma volume and thiocyanate space determinations were made from six-point disappearance curves using a Coleman Model 6 spectrophotometer.

TABLE I.—*Experiment W. L.—Daily Salt Balance*

Experimental Period	Day of Experiment	NaCl Intake (Gm.) Diet	Tablets	As 0.9% Intravenous NaCl	Total	Gastric NaCl Output: Gastric Washings cc./day	Gastric NaCl Concentration (Gm./L)	Gastric Total Gm. NaCl/day	Urine NaCl Output: cc./day	Urine NaCl Concentration (Gm./L)	Urine Total Gm. NaCl/day	NaCl Output (Gastric Plus Urine)	NaCl Balance (Intake Minus Output)
Control	1	0.84	5	0	5.8	—	—	—	2,210	3.7	8.2	8.2	— 2.4
	2	0.87	3	0	3.9	—	—	—	975	3.3	3.2	3.2	+ 0.7
	3	1.17	3	0	4.2	—	—	—	735	3.5	2.6	2.6	++ 1.6
Depletion	4	0	0	0	0	3,250	3.34	10.9	735	2.0	1.5	12.4	—12.4
	5	0	0	0	0	10,850	1.25	13.5	490	0	0	13.5	—13.5
	6	0	0	0	0	6,410	0.92	5.9	425	0	0	5.9	— 5.9
	7	0	0	0	0	2,900	0.96	2.8	605	0	0	2.8	— 2.8
Replacement	8	0.49	0	4.5	5.0	—	—	—	1,170	0	0	0	+ 5.1
	9	0.63	0	4.5	5.1	—	—	—	2,140	0	0	0	+ 5.0
	10	0.87	0	4.5	8.0	—	—	—	2,495	0	0	0	+ 5.4
	11	1.20	0	6.8	9.8	—	—	—	1,990	0	0	0	+ 8.0
	12	0.84	0	9.0	9.9	—	—	—	1,980	0	0	0	+ 9.8
	13	0.87	0	9.0	9.9	—	—	—	1,240	0.3	1.3	0.3	+ 9.6
	14	1.20	0	9.0	10.2	—	—	—	1,910	1.8	1.8	1.8	+ 8.4
	15	0.87	0	9.0	9.9	—	—	—	2,270	4.7	4.7	4.7	+ 5.2

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Hematocrits were measured in quadruplicate by centrifugation at 3000 RPM for 45 minutes. Plasma total protein concentrations were determined by the copper sulfate specific gravity method of Phillips, et al.[9]

Other measurements were: body weight, urine pH, urine specific gravity, urine CO_2, plasma CO_2, and plasma total base concentration. The measurements pertaining to acid-base balance will be presented in a subsequent publication.

All measurements were made daily except plasma volume and thiocyanate space. These were measured about every other day.

EXPERIMENTAL RESULTS

Examination of Figure 5 and Table I, II, and III show that the subject was in good salt balance during the preliminary control period; plasma chloride concentration varied ±2%, urine chloride ±6; total extracellular salt estimations were 103 and 101 Gm.

TABLE II.— *Experiment W. L.—Chloride Measurement*

Experimental Period	Day of Experiment	Plasma Chloride Concentration (mEq/L)	Plasma Chloride Concentration (mg % NaCl)	Plasma Chloride Concentration % Control	*Total Plasma NaCl Content (Gm./NaCl)	†Total Thiocyanate Space NaCl Content (Gm./NaCl)	Urine NaCl Concentration (Gm./L)	Urine NaCl % Control Concentration
Control	1	106.0	620	ave. =		102.9	3.7	ave. =
	2	102.4	599	100%	—	—	3.3	100%
	3	103.8	607		15.5	101.0	3.5	
Depletion	4	103.4	605	100.0	—	—	2.0	57
	5	97.6	571	94.2	14.0	86.2	0	0
	6	88.6	518	85.5	11.0	73.0	0	0
	7	81.2	475	78.4	—	—	0	0
Replacement	8	78.4	459	75.7	9.0	69.8	0	0
	9	80.4	470	77.6	—	—	0	0
	10	86.2	509	83.2	12.5	73.8	0	0
	11	89.6	524	86.5	—	—	0	0
	12	93.6	548	90.3	15.6	—	0	0
	13	98.0	573	94.6	—	—	0.3	0.7
	14	101.6	594	98.1	—	120.6	1.0	27
	15	107.0	626	103.3	—	—	2.1	60
	16	107.4	628	103.7	23.2	130.6	—	—

* Total plasma salt content = plasma NaCl concentration × plasma volume
† Total thiocyanate salt content = plasma NaCl concentration × thiocyanate space volume.

During the four days of gastric suction there was a daily negative salt balance of —12.4 Gm., —13.7 Gm., —5.9 Gm., and —2.8 Gm.; a total of 34.8 Gm. of salt loss in four days. Salt replacement was completed on the sixth day of the replacement period, 33.2 Gm. NaCl having been replaced at the end of the fifth day and a total of 43.1 Gm. by the end of the sixth. The positive salt balance during the final three days represents a retention in excess of that lost during the depletion period.

During the first day of gastric suction, extracellular salt content decreased 15 Gm., a loss equal to the total amount of salt normally present in this subject's plasma. Despite this salt depletion, plasma chloride concentration fell

only 6%, while on the other hand, urine chloride concentration fell to zero and remained zero. These figures show that the moderately severe salt depletion was quickly apparent from the decrease in urine chloride concentration while it was scarcely detectable from the plasma chloride concentration determinations. The plasma chloride concentration was being maintained by cessation of chloride excretion in the urine.

At the end of the depletion period, plasma chloride concentration was 459 mg. %, a fall of only 24% below normal control concentration. At this time the extracellular salt content had fallen 32 Gm. below normal, this figure checking well with the 34.8 Gm. of NaCl recovered from the gastric fluid and

TABLE III.—*Experiment W. L.—Miscellaneous Data*

Experimental Period	Day of Experiment	Body Weight (Kg.)	Spun Hematocrit, Percent	Total Blood Loss by Venapuncture (cc.)	Total Plasma Protein (Gm. %) Gm./cc.	Plasma Volume (cc.)	Thiocyanate Space (cc.)	Urine Sp. Gr.
Control	1	63.20	45.0	50	6.29	—	16,600	1.009
	2	62.50	48.5	62	6.69	—	—	1.004
	3	63.15	45.4	112	6.29	2,560	16,600	1.020
Depletion	4	53.00	44.5	124	6.30	—	—	1.014
	5	59.10	48.0	174	7.35	2,460	15,100	1.031
	6	57.50	51.4	224	—	2,120	—	1.027
	7	57.10	54.1	236	8.60	—	—	1.022
Replacement	8	56.55	52.5	286	7.26	1,950	15,200	1.019
	9	57.40	—	298	7.36	—	—	1.009
	10	58.90	41.7	348	6.65	2,460	14,500	1.007
	11	58.20	41.8	360	6.28	—	—	1.008
	12	59.40	39.4	410	6.22	2,850	9,800	1.007
	13	59.75	37.8	422	5.74	—	—	1.013
	14	60.45	33.6	472	5.03	—	20,300	1.008
	15	61.00	34.0	484	5.03	—	—	1.008
	16	61.50	33.4	534	5.03	3,700	20,800	—

NB—The following daily observations will also be reported in a future publication; Plasma CO_2, plasma total base, urine pH and urine CO_2

urine, and corresponding to one-third of the normal extracellular salt content, and twice the normal plasma salt content. This fall in plasma chloride concentration indicated a serious alteration in extracellular isotonicity. Clinically, the subject was lethargic, fainted on rising from bed, his eyes appeared sunken, the skin became loose and dry and scaley. Despite this extreme water and salt depletion, the plasma chloride concentration never fell as low as had the urine chloride concentration during even the first day of depletion.

The fall in urine volume to a minimum of 425 cc. per day would be expected in this state of "mixed" water and salt depletion. Reduction in both urine volume and urine chloride concentration indicate a mixed depletion requiring both salt and water therapy.

During the third part of this experiment, water was restored by free oral intake while salt restoration was accomplished by a low salt diet supplemented

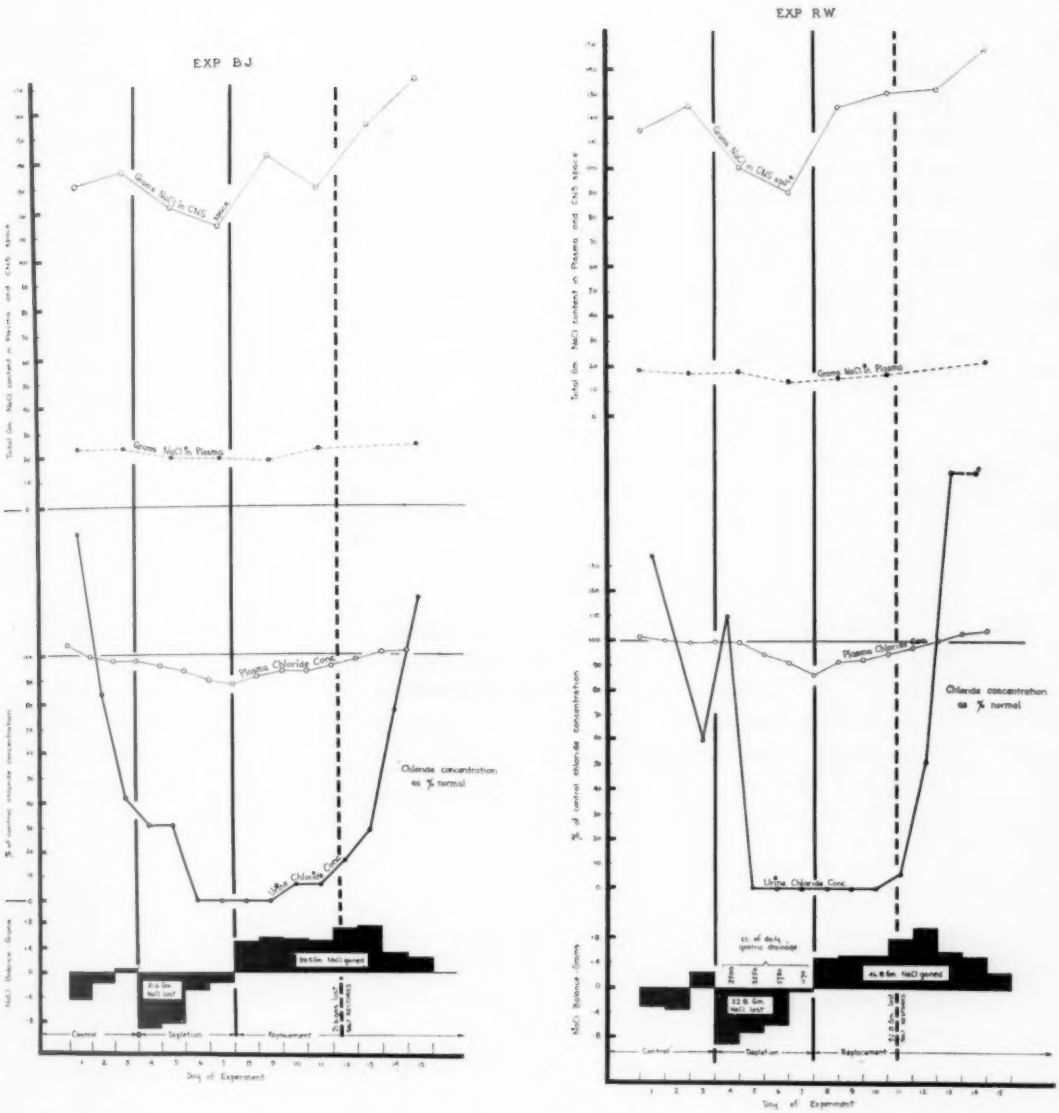

FIG. 6.—Showing experiments identical to that of Figure 5. The results are confirmatory.

by intravenous 0.9% saline. Salt replacement was completed during the early part of the sixth day. At this time (see vertical broken line on Fig. 5) the extracellular and plasma salt contents had returned to normal, chloride reappeared in the urine, but plasma chloride concentration had returned to only about 95% normal. Continuation of daily infusions of 1000 cc. 0.9% saline during the final four days caused a rapid increase in extracellular salt content and urine chloride concentration, and by the time plasma chloride concentration returned to normal, the total number of grams of salt in the extracellular fluid was 120% of the amount observed in the preliminary control period.* That this actually represents a subclinical edema is confirmed by the hematocrit and total protein concentrations; both fell to 20% below normal (corrected for experimental red blood cell and protein loss). Apparently urine chloride concentration better indicated salt replacement than did plasma chloride concentration; for chloride reappeared in the urine as soon as the 34.8 Gm. body salt deficiency was replaced, while return of plasma chloride concentration to normal was accompanied by overloading of the extracellular space with salt and water.

This experiment indicates a renal threshold level of about 95% normal plasma chloride concentration. Below this concentration chloride did not appear in the urine. It supports the physiologic hypothesis presented earlier in this paper and demonstrates the advantages of urinary over plasma chloride analysis.

Figure 6 represents similar studies carried out on the two other volunteer subjects. The results are similar to those discussed above. There was a renal threshold level of about 95% normal plasma chloride concentration. Below this level, chloride did not appear in the urine. The urine chloride concentration was a much more sensitive indicator of salt depletion and replacement than was the plasma chloride concentration. Continuation of saline infusions after chloride appeared in the urine caused excess salt and water to be retained in the extracellular space.

DISCUSSION

A slight discrepancy between the experimental observations published here and those reported earlier from this laboratory[10] is to be noted. It was observed in dogs that "When a condition of salt depletion is being established, drop of chloride excretion to a low rate is a more sensitive indicator of the condition than is the plasma chloride concentration. But when the condition of depletion of the type caused by loss of gastric juice is in process of correction by NaCl administration, restoration of normal plasma chloride concen-

* The changing thiocyanate space volume in this experiment is not a cumulative technical error resulting from accumulation of repeated thiocyanate dosage. This was proven by repeating the series of thiocyanate determinations in this same subject while in a normal state six months after the experimental period. Thiocyanate space measurements every other day for two weeks gave the following volumes: 15.5L, 15.0L, 18.2L, 17.9L, 17.3L, 16.3L, 17.4L, 17.9L.

tration shows more accurately than resumption of chloride excretion when enough saline has been given to correct the condition." During salt replacement there was a lowered renal chloride threshold in the dog experiments, but this was not observed in the experiments on man.

This discrepancy is best explained by the great difference in experimental conditions. In the dog experiment reported, salt replacement was conducted rapidly, i.e., 1 Gm. NaCl per pound body weight during 12 hours, and there was a diuresis of the accompanying dextrose and water infused. A single massive intravenous infusion was given. Salt replacement in the human experiment was accomplished slowly over five to six days, no rapid infusions were given, nor was diuresis stimulated.

The present work does confirm the previous observations[10] that an internal alkalosis resulting from hypochloremia may be accompanied by the excretion of an acid urine. Such a paradoxical concurrence was invariably present in the present experiment. Measurements of urinary pH, urinary CO_2, plasma CO_2, and plasma total base concentration of this and other subjects will be reported in the future.

CONCLUSIONS

There is sufficient evidence both in the literature (11, 12, 13, 14, 15, 16) and in our experiments on human volunteers to justify suggesting that, providing kidney and adrenal function are normal, *water and salt balance will be properly maintained if daily urine volume exceeds 1500 cc. and urine salt concentration approximates 3 Gm. per liter.* Since urine volume and approximate salt concentration are simple bedside determinations, they have been found very useful as routine guides to parenteral water and salt administration. It is fortunate that these guides are at the same time most informative and simple to determine, and are thus admirably adapted to clinical use.

There is a discrepancy between the above conclusions and the data presented in Figure 5. Figure 5 shows that chloride reappears in the urine as soon as salt restoration is complete (vertical broken line) and that increasing urine salt concentration is accompanied by excessive water and salt retention. This observation is confirmed in the other experimental subjects. Despite this experimental observation, it is recommended that salt balance will be best maintained if urine salt concentration is maintained at about 3 Gm. NaCl per liter. Limited clinical observations suggest that salt deficiency is apt to occur if one attempts to keep urine salt concentration slightly above zero; it has been easier and safer to maintain about 3 Gm. per liter urinary salt. Clinical studies of Bartlett et al[11] are in agreement with the experimental findings presented here. They recommended that, when their "volume for volume" rule cannot be followed, urinary chloride excretion be maintained at one or less grams per day, although such procedure may result in slight chloride depletion and fall in plasma chloride concentration. On the other hand, Hadden[12, 15] recommends that saline infusions be given until the urine contains 5-10 Gm. of NaCl in 24 hours. Sauchez-Vegas and Collins[14] agree with Hadden. Those recommending minimum urinary salt excretion do so in

fear of salt retention, while those recommending relatively great salt excretion fear salt depletion. A compromise seems advisable and agrees with the recommendation that urinary salt concentration be kept at about 3 Gm. per liter and urinary output at about 1500 cc. per day. Further clinical observations will decide whether these recommendations are optimum.

Urine salt concentration rather than daily salt excretion is recommended with the realization that the latter is probably a more accurate guide to salt administration. However, the determination of daily salt excretion necessitates the inconvenience of measuring the salt concentration of aliquot samples of twenty-four-hour urine collections. Furthermore, it is convenient to measure the urine salt concentration at the bedside just before starting each infusion, and to administer dextrose solution if there is more than 3 Gm. of salt per liter of urine, or saline solution if there is less than 3 Gm. per liter.

It is also suggested that urine salt concentration determination may be used to detect the presence or absence of body salt depletion. If the Fantus test is used and one drop of silver nitrate turns the urine-potassium chromate mixture red, one may assume that salt depletion is present; and, conversely, when there are at least 3 Gm. of salt per liter of urine, saline therapy is rarely indicated.

Thus the information obtained from urine NaCl concentration measurement at the bedside or in the emergency room is valuable in deciding whether or not the patient needs salt therapy, while measurement of urine volume excretion is valuable in deciding whether or not the patient needs water therapy. We must not place complete dependence on these simple measurements as quantitative guides to such a complicated physiological mechanism as water and salt equilibrium. These guides must be supplemented by clinical observations of edema, skin turgor, thirst, respiration, the appearance of the tongue and eyeballs, mental state, etc.

It is not suggested that plasma chloride determinations be discarded. As salt depletion progresses, salt first disappears from the urine and then plasma chloride concentration continues to fall. Once the urine has become salt free, plasma chloride concentration must be determined in order to estimate the magnitude of salt depletion. If plasma chloride concentration is abnormally low, plasma CO_2 concentration must be measured.

In the presence of decreased kidney function it is probably safer to depend on plasma chloride than on urine salt measurements; poorly functioning kidneys may fail readily to excrete salt. There is evidence indicating that renal function may be depressed in conditions causing diminished blood volume, as in dehydration, during and immediately following shock, and immediately postoperatively. Further studies are needed before urinary salt determinations can be recommended in these conditions.

At present there is discussion in the literature concerning the concentration of saline to be infused intravenously. Further discussion is intentionally avoided here, for it is the purpose of this paper to separate dehydration into two categories, water depletion and salt depletion, and to recommend that

each type of depletion be treated separately. Discussion of electrotlytes other than NaCl is also avoided in this paper, although it is understood that simple NaCl therapy is frequently incomplete electrolyte therapy.

SUMMARY

It is suggested that the loose term "dehydration" be substituted by its physiologic components: "primary water depletion," "primary salt depletion," and "mixed water and salt depletion." The physiologic basis for this recommendation is presented as well as the reasons for using urine salt (measured as chloride) concentration and urine volume instead of plasma chloride concentration as a guide to the diagnosis and treatment of these various types of dehydration. An experimental study of volunteer subjects is presented in support of this recommendation.

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DISCUSSION.—DR. I. S. RAVDIN, Philadelphia: These studies represent the type of work which is necessary to provide a clearer knowledge of the fluid and electrolyte requirements of surgical patients. In adopting Marriott's classification which divides dehydration into two conditions that differ in cause in physiologic and chemical effects,

and in the treatment needed, they have provided a more rational concept of the problem of dehydration and they have further strengthened our thinking by calling these conditions "primary water depletion" and "primary salt depletion." Anyone who has attempted to study the shifts in fluids and electrolytes in man, in health and in disease, knows that most of the methods now being utilized provide meagre data on what is happening in the body as a whole, and in the specific compartments which go to make up the whole. The part which the normal kidneys play in their effort to maintain isotonicity of the plasma and interstitial fluids was stressed some years ago by James Gamble and his associates. It should be recognized that urinary analyses such as Dr. Evans and Dr. Van Slyke are making are particularly useful when the kidneys are normal. The conditions initiating primary water and/or salt depletion, however, frequently result in a variable degree of renal injury, as Dr. Campbell and Dr. Coller and their associates have shown. Under such conditions, the authors have rightly pointed out that the urine may not correctly indicate the internal conditions of salt and water content. In the seriously ill surgical patient, abnormalities in glomerular infiltration, tubular secretion and absorption, exist all too frequently. It is in these patients that the excretion of an apparently normal urinary volume may be associated with marked abnormality in base, chloride and other electrolyte excretions. Under such circumstances it may be far better to be very cautious in the administration of large amounts of fluid or salts, as Dr. Coller pointed out in his discussion. This is especially true in nephrosclerosis or in kidneys subjected to periods of anoxia. It may be better to keep the patient in a state of mild hypochloremia than to risk the untoward effects of the burden which the opposite state may impose on the patient.

There remains much to be learned about the function of the kidneys in health and in disease, of the effect of the different renal components on various salts and especially such salts as potassium salts and calcium salts. In certain conditions there is generalized renal impairment, but tubular and glomerular dysfunction are not necessarily impaired to the same degree. The entire picture may be further complicated by abnormalities in plasma protein; for in severe hypoproteinemia there is apt to be specific sodium retention. Studies of the type reported in the last two papers facilitate greatly our thinking upon the problems of renal and will, we hope, provide a more rational basis for parenteral fluid and salt therapy in surgical patients.

Dr. John H. Gibbon, Jr., Philadelphia: I think Dr. Coller's warning that patients with anuria should be kept on the "dry side," merely replacing insensible water loss, is a very important one. Kolff of Holland, who developed an apparatus for the dialysis of blood outside the body, is in hearty agreement with this point of view. These patients will often recover provided they are not drowned by excessive amounts of intravenous fluid and provided the acid base equilibrium is maintained. I think the observation on the great loss of salt and water which occurs during the period of diuresis, is very interesting.

Drs. Evans and Van Slyke are to be congratulated on a beautiful piece of work in carrying out experiments on normal human subjects and presenting us with a very practical test for determining what we all want to know at the bedside, i.e., whether we should give a patient salt solution, or glucose and distilled water, intravenously.

Dr. Kenneth N. Campbell, Ann Arbor: This paper brought out extremely important factors which Dr. Van Slyke did not have time to emphasize. The first of these is the fallacy of basing therapy on a laboratory value. May I give very concrete examples: I speak particularly of laboratory values for plasma chloride. If we take the normal plasma volume at 3000 cc., and order a plasma protein determination from the laboratory that comes back some 7 Gr. per cent, that would give us a total circulating protein in our plasma of some 210 Gm. Now, if perchance that individual did not have a normal plasma volume, let us say he had been subjected to dehydration or to plasma loss from some other cause, we might receive back from

the laboratory a plasma protein value of eight grams per cent at a time when the plasma volume was not 3000 cc. but 2000 cc. With simple arithmetic that will tell you that we now have only 160 Gm. of total circulating protein and not 210. Our laboratory value is higher, it is better than the example I gave you previously, and may lead one very erroneously into assuming that that patient has a normal total circulating protein. Similar changes may occur obviously in determinations of chlorides.

We are very happy to hear of the experimental work that Drs. Evans and Van Slyke have reported concerning the interpretation of plasma chloride values. They have simplified it to its utmost on a rational basis.

I will finish by saying something about volume for volume replacement which we have heard so much about in the past. If one institutes gastric or intestinal drainage and replaces volume for volume the secretions obtained with the solutions we now have available, and we call those normal physiologic solutions—when they are not either normal nor physiologic—you may be replacing approximately twice the amount of salt that you are withdrawing from your intestinal or gastric drainage.

DR. E. I. EVANS, Richmond, Va. (closing): We should like first to thank Dr. Ravdin for his comment. I should like then to say that I was much impressed by the remarks made by our President this morning about teaching surgery to medical students. I refer to this now because of what we have learned by placing in the hands of the medical student this simple bedside urine chloride technic, so that they may follow their patients day by day and learn thereby the fundamentals of fluid balance and salt therapy. We get almost every week requests from new groups of students on the ward for these little laboratory beside kits so that they can run urine chlorides on their own patients. It is gratifying for a teacher to learn how easy it is to get a little idea across once a year or so.

Third, I am happy that Dr. Lockwood brought up the important point potassium deserves in his reference to Dr. Darrow's work. It is rather interesting in observing cycles of surgical research how often different groups become interested in the same type of thing at about the same time. We are following with interest what Dr. Lockwood's group is doing. We have come to similar conclusions and have learned a great deal from Dr. Darrow's presentations.

It is well here to call attention to the extreme danger of giving adrenal cortical hormone to those surgical patients who are suffering from hypochloremic alkalosis. We have learned that one cannot correct this alkalosis by administration of salt or Ringer solutions if at the same time one is administering even small amounts of adrenal cortical hormone.

About the "dry" side. We agree, Dr. Campbell, with everything you say, but I cannot sit down without emphasizing again, be "dry" on the side of sodium chloride or water, but don't be "dry" on the side of whole blood when it is needed.

STRESS, STRAIN AND SUTURES*

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SALT LAKE CITY, UTAH

TWO BRIDGES ARE ILLUSTRATED in Figure 1: One is constructed without definite knowledge of the strength of component parts and without consideration of the load to which it may be subjeced; the other, in contrast, is a product of engineering skill and art in which the strength of every bolt and cable, strut, beam and column is known, where each structural part is adjusted to meet calculated stresses and strains with ample margins of safety. What will happen to the toy bridge when Junior steps on it is anybody's guess, but the safety of the engineer's bridge is no guesswork; every day thousands of people unhesitatingly entrust their lives to it.

In operative surgery there are also potentially dangerous stresses and strains and practical problems of mechanical forces. It is often literally true that the life of a patient hangs by a thread.

The tensile strength of sutures, in the strand and at the knot, depends upon the size of the thread and the material of which it is composed. (Fig. 2). Given the same material, tensile strength varies with the square of the diameter of the thread; double the diameter and you quadruple the strength. Knot breaking strength, as a rule, is about 70 per cent of the tensile strength of the strand away from the knot. Brittle material like silkworm gut is relatively weak at the knot. Size for size, the weakest suture material is wet catgut. This material is distinctive also in that, after implantation in tissues, it rapidly loses what strength it has.

Table I shows how badly is needed a uniform gage for all suture material. A gage, based, let us say, upon thousandths of an inch diameter would enable the surgeon, by quick reference to an appropriate chart, to determine the tensile and knot-breaking strength of any given thread, and to suit the sort and size of sutures to his immediate purposes.

The strength of sutures depends not alone upon the tensile strength of the strand, but also upon the security of the knot. Each of the horizontal stripes in Figure 3 represents a set of 20 tests. None of the five commonly used knots represented there is safe when the ends are cut very short; indeed, the only dependable knots are those with three throws, the ends being cut 2 or more mm. long. Similar results are obtained with cotton (Fig. 4); nor is the pattern of these tests altered significantly by wetting the thread with water or serum, by waxing or oiling the thread, or by using boiled or autoclaved thread. Results with catgut are much the same (Fig. 5). Steel wire knots are very prone to slip. Particularly unreliable are those knots which tighten down when the second throw is pressed home, and the knot which ends-off a continuous suture, in which two strands are tied to one.

* Read before the American Surgical Association, May 27, 1948, Quebec, Canada.

TABLE I.

COMPARATIVE SIZE (DIAMETER) OF SUTURE MATERIAL

Diameter $\frac{1}{1000}$ inch	CATGUT		SILK		NYLON		COTTON		WIRE	
	Dry	Wet	Surgical	Commercial	Surgical	Commercial	Surgical	Commercial	Tantalum	Steel
28		No. 1								No. 22
26										
25	No. 2		No. 2							
24		No. 0								
23					No. 3					
22	No. 1				No. 2					No. 24
21										
20			No. 1							
19	No. 0	No. 00								
18										No. 26
17							"C"			
16	No. 00							"8"		
15			No. 0					"10"		
14		No. 000								No. 28
13					No. 00		"8"	"20"		
12	No. 000							"30"		No. 30
11		No. 4-0								
							"A"			
10			No. 000		No. 000		No. 0	"40"		
9	No. 4-0	No. 5-0						"50"		No. 32
	No. 5-0							"60"		
8			No. 4-0	"A"		"A"	No. 000	"80"		
7										No. 34
			No. 5-0							
6										
5									.005 in.	No. 35
4			No. 6-0							No. 36
3									.003 in.	

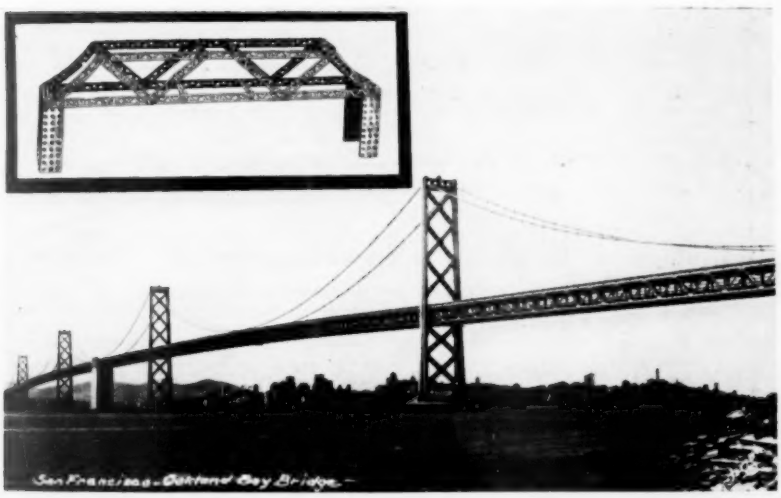

FIG. 1.—A splendid example of engineering skill, contrasted with a toy bridge (inset) which is constructed without regard to principles of engineering.

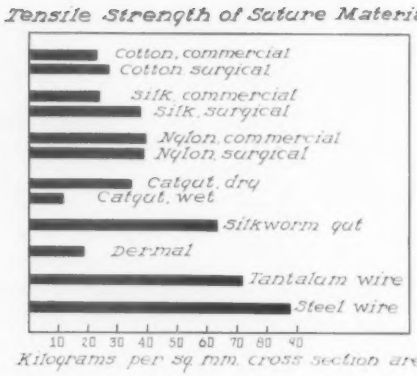

FIG. 2.—Relative tensile strengths of suture materials.

Actually in surgery we deal with loops rather than straight strands. The strength of a simple loop is double that of a straight strand (Fig. 6), and a double loop is four times as strong, presumably because of distribution of tension and friction against the tissues.

In surgery, loops are subject not only to the longitudinal pull indicated in Figure 6, but also to intraloop tensions. For example, a ligature placed around an artery (Fig. 7A) must withstand bursting forces due to the pressure of the blood within the vessel and the expansile elasticity of the arterial wall, and this stress is transmitted to the knot.

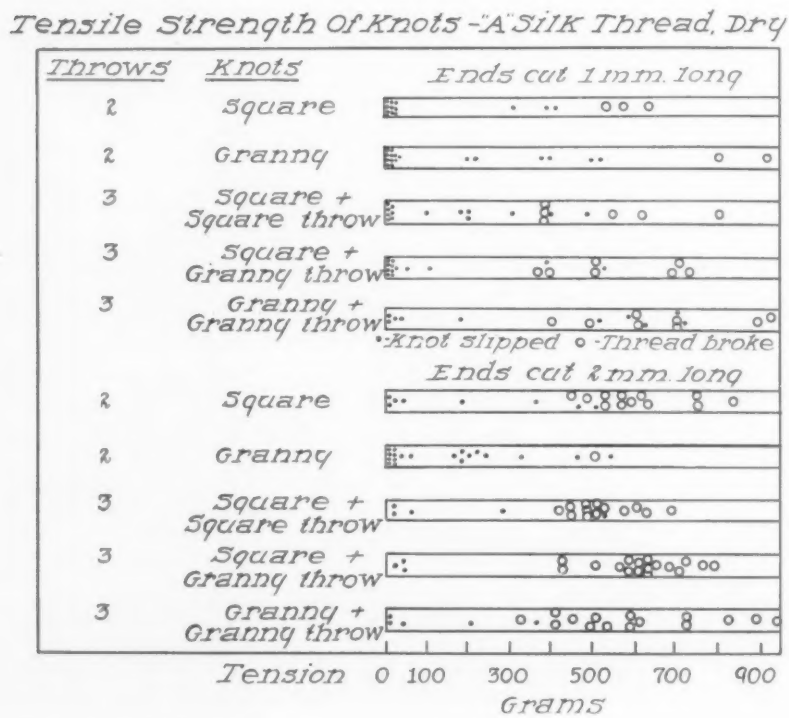

FIG. 3.—Strength and security of knots. Tests made with a tensiometer. Solid dots represent knots which came untied; circles knots which held until the thread broke. The amount of tension required to loosen or break the knot is indicated by the position of the dot or circle.

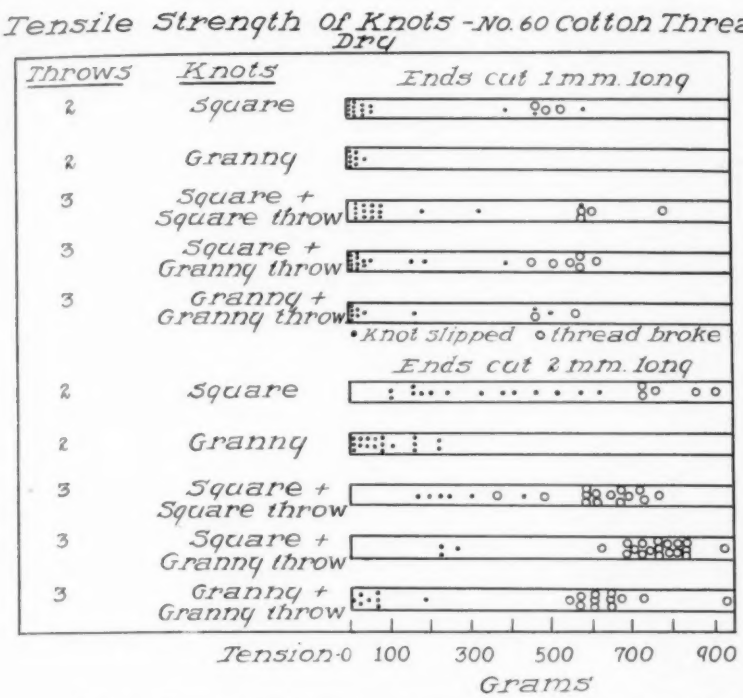
Tensile Strength Of Knots - No. 60 Cotton Thread, Dry
Throws
Knots
Ends cut 1 mm. long
2 Square
2 Granny
3 Square + Square throw
3 Square + Granny throw
3 Granny + Granny throw
• Knot slipped ○ thread broke
Ends cut 2 mm. long
2 Square
2 Granny
3 Square + Square throw
3 Square + Granny throw
3 Granny + Granny throw
Tension 0 100 300 500 700 900
Grams

FIG. 4.—Strength and security of knots. Size "A" silk thread, commercial grade.

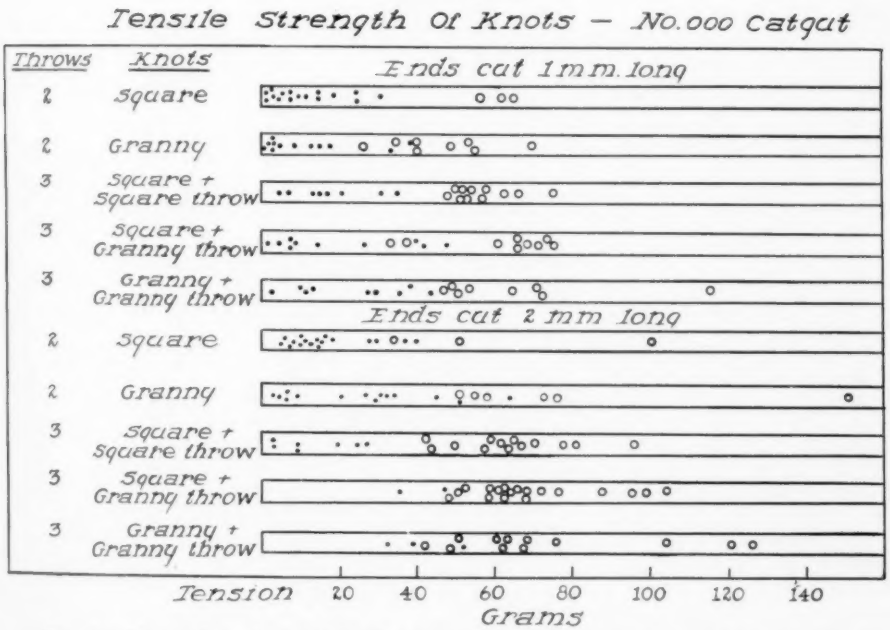

FIG. 5.—Strength and security of knots. No. 000 catgut. Catgut in general is less uniform than other suture material in tensile strength of the strand and in knot-holding ability. Simiular results were obtained with plain and chromic catgun.

Figure 7B illustrates schematically the bursting forces felt by an abdominal incision. The suture represented there has to withstand the cumulative effects of (1) intra-abdominal pressure, (2) the lateral pull of abdominal muscles, and (3) edema or inflammatory pressure within the loop itself. A similar combination of tensions acts also upon lines of suture in the stomach or intestine.

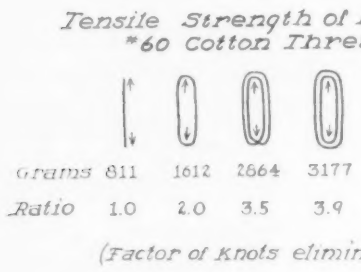

FIG. 6.—Strength of loops.

The bursting strength of a loop is inversely proportional to the area which it encloses; or, to put it more accurately, the tension is proportional to the area which it encloses; or, to put it more accurately, the tension is proportional to the area enclosed. The results shown in Table II were obtained in tests made upon pneumatic tubes and balloons of various sizes, but this law of mechanics, well known to hydraulic engineers, applies to animal tissues also and has wide applications in surgery. Mass ligatures are more apt to break or come untied than ligatures around small bleeding points or isolated vessels (Fig. 8). Large sutures are subject to greater tensions than small sutures. Four-zero silk is more than strong enough to tie a small artery like the thyroid, but might not hold the external iliac artery. The

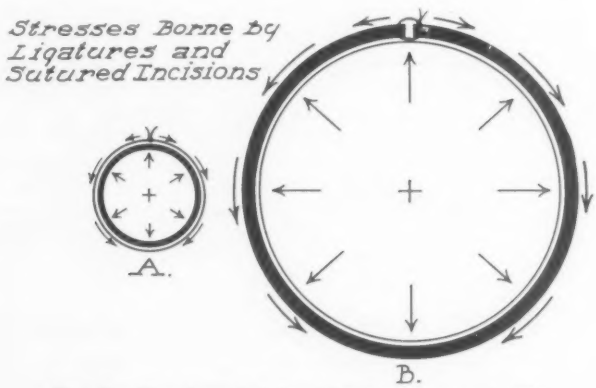

FIG. 7.—Tensions felt by (A) ligatures and (B) sutured incisions.

larger the diameter of an organ or cavity, the greater the tension upon sutured incision (Fig. 9).

It follows that the size of suture and ligature material should be selected with a view to the tensions to which it may be subjected. The finest available cotton or silk thread should suffice to ligate ordinary bleeding points.

The operator who places small, closely spaced sutures can afford to use fine suture material, whereas the operator who habitually takes large bites widely spaced must needs use coarser thread. A perforated peptic ulcer is more safely closed with two or three mattress sutures than with a relatively large purse-string suture.

This brings us to a consideration of rows of sutures. Tensions experienced by individual sutures are not easily measured in patients, but they

TABLE II—*Strength of Loops of No. 60 Cotton Thread Around Pneumatic Tubes or Balloons (Knots with many throws to prevent slipping)*

Diameter of tube or balloon	Pressure required to break thread	π (the Greek letter "pi," i.e., 3.1416) x pressure
2.77 cm.	250 mm. Hg.	1505
3.44	204	1897
4.71	82	1426
8.81	22	1344
17.4	6.5	1355
24.0	3.5	1580

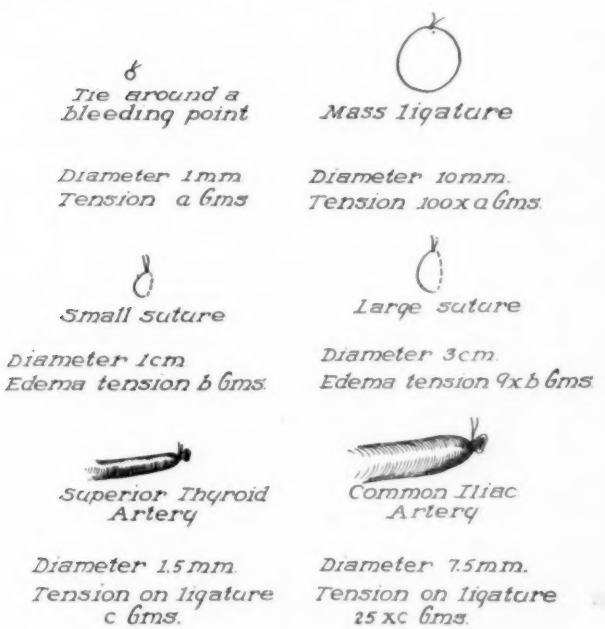

FIG. 8.—Other factors being equal, tensions on ligatures and sutures vary with the cross-section area enclosed by them.

can be studied in models and in freshly killed experimental animals, in which all the mechanical forces concerned are reproduced; and there can be little doubt that the effects observed in such experiments are similar to those which obtain in the living body. When sutures are uniformly spaced, the total tension felt by the suture line is found to be distributed equally

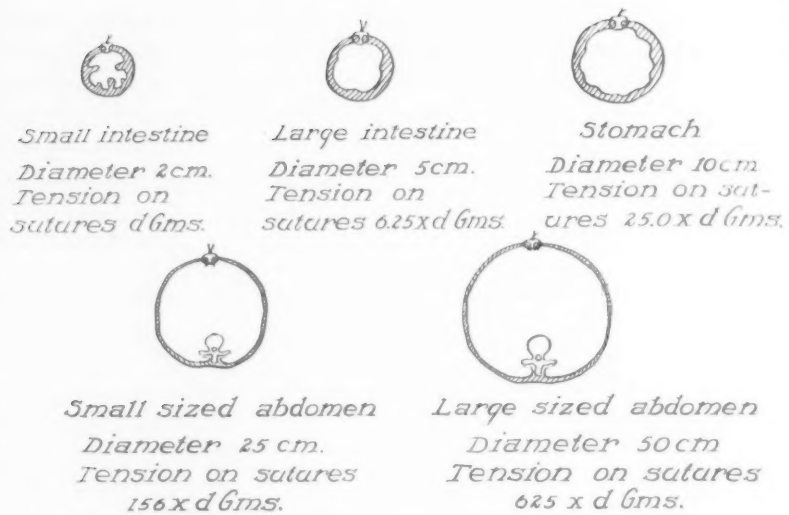

FIG. 9.—Effect of size of an organ or cavity upon the tension of sutured incisions. The values indicated in this diagram are used simply to illustrate the principle under discussion; actually, the total tension of sutured incisions is a complex matter with many variable factors involved.

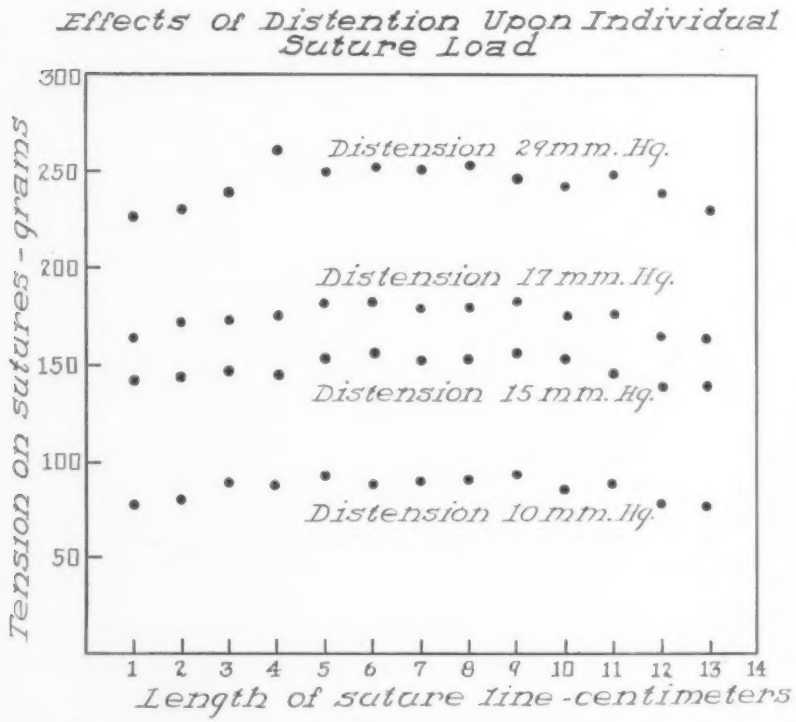

FIG. 10.—Distribution of tension between sutures in an incision, and effects of distension upon the suture load.

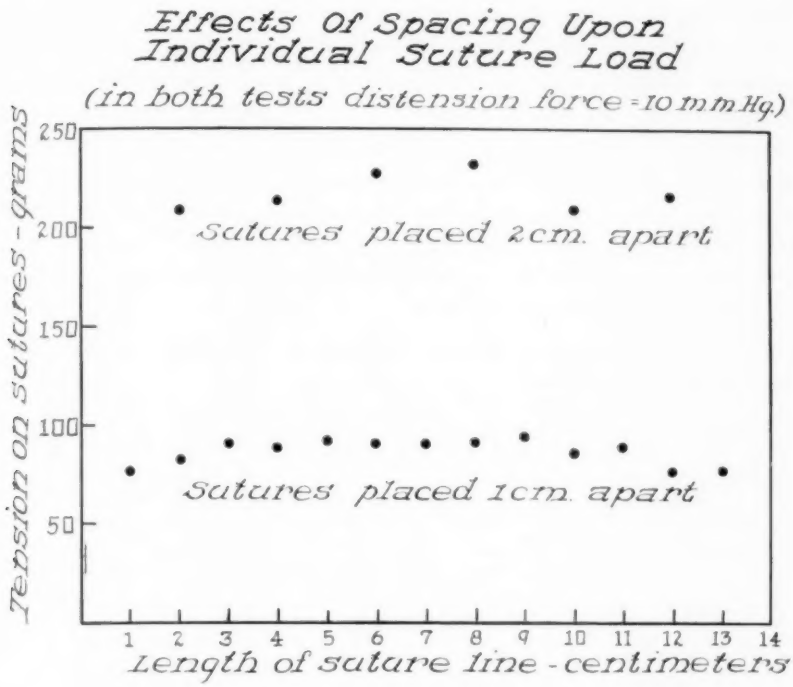
Effects Of Spacing Upon
Individual Suture Load
(in both tests distension force = 10 m m Hg.)
Tension on sutures - grams
250
200
150
100
50
Sutures placed 2 cm. apart
Sutures placed 1 cm. apart
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Length of suture line - centimeters

FIG. 11.—Effect of spacing of sutures upon suture load.

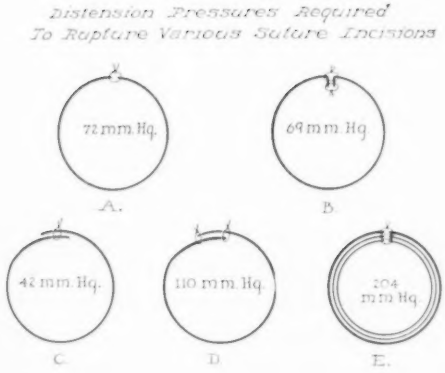

FIG. 12.—Results of tests made under comparable conditions to show the relative strengths of various sorts of closure. A, a single row of approximating sutures; B, a second, "reinforcing" row of invaginating sutures; C, imbrication with a single row of sutures; D, imbrication with two rows of sutures; E, 3 layers closed independently.

between the sutures (Fig. 10). In the case of an abdominal incision, the greater the intra-abdominal pressure, the greater the tension upon the entire suture line, and the greater the tension upon each individual suture. If there are fewer sutures more widely spaced, each suture then has to carry a larger share of the total load (Fig. 11).

Other factors being equal, the over-all tension on an incision is proportional to its length. There are usually more sutures in a long incision to share the load, however, so that the tension upon individual sutures is apt to be much the same, whether the incision is long or short. Should one suture

of a row slip or break, the tension which it has borne is immediately transferred to its neighbors. If, with the sudden increase in tension, those sutures break also, even greater strain is then thrown upon the next in line. Thus a sort of "chain reaction" may be set up with disruption of the entire row of sutures.

Figure 12 shows diagrammatically the relative strengths of various closures by layers. In the so-called reinforcing row (Fig. 12B), all of the tension is concentrated on the outer row; should that give way, the full force is then thrown on the inner row. The main advantange of that sort of closure is watertightness. Imbrication does not add to strength unless both edges are sewed down A closure with three independent layers is three times as strong as a single layer closure.

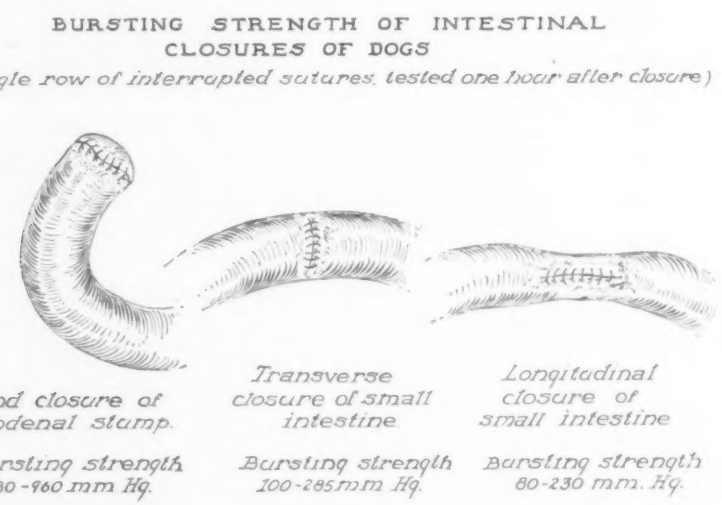
BURSTING STRENGTH OF INTESTINAL CLOSURES OF DOGS
(Single row of interrupted sutures, tested one hour after closure)
End closure of duodenal stump.
Bursting strength 280-960 mm Hg.
Transverse closure of small intestine
Bursting strength 100-285 mm Hg.
Longitudinal closure of small intestine
Bursting strength 80-230 mm. Hg.

FIG. 13.—Bursting strength of intestinal incisions in dogs. Not infrequently in these tests the wall of the intestine ruptured before the suture line gave way or leaked.

Experiments in dogs show that a duodenal stump closed with a single row of well-placed, interrupted, inverting sutures of No. 60 cotton or 4-0 silk thread (Fig. 13) is able, without leakage or disruption, to withstand intraduodenal pressures of 280 to 960 mm. Hg.—pressures far in excess of anything ever encountered clinically. I am convinced that leakage of the duodenal stump is due not so much to weakness of sutures as to ischemia, necrosis, and cutting through of sutures, either because they were tied too tight, or because too much bowel wall was turned in and strangulated with multiple rows of sutures.

Since the transverse or cross section stretch of the bowel exceeds the longitudinal stretch (Fig. 13), intestinal distention puts less strain on transverse than on longitudinal incisions. For that reason end-to-end anastomoses are mechanically stronger than side-to-side anastomoses.

Another aspect of the problem is strength of tissues. Unless the tissue sewed is as strong as the suture used, variations in suture strength become irrelevant. Three variable factors must be considered in this connection. First, the sort of tissue one has to deal with. Skin and fibrous tissue are the toughest of the soft tissues; indeed, the suture-holding strength of most soft tissues depends upon the amount of fibrous tissue they contain. Thus the brain and spinal cord, containing minimal amounts of fibrous tissue, will scarcely support sutures, but the sutured sheath of a peripheral nerve will hold even under considerable tension. The seromuscular coat of the

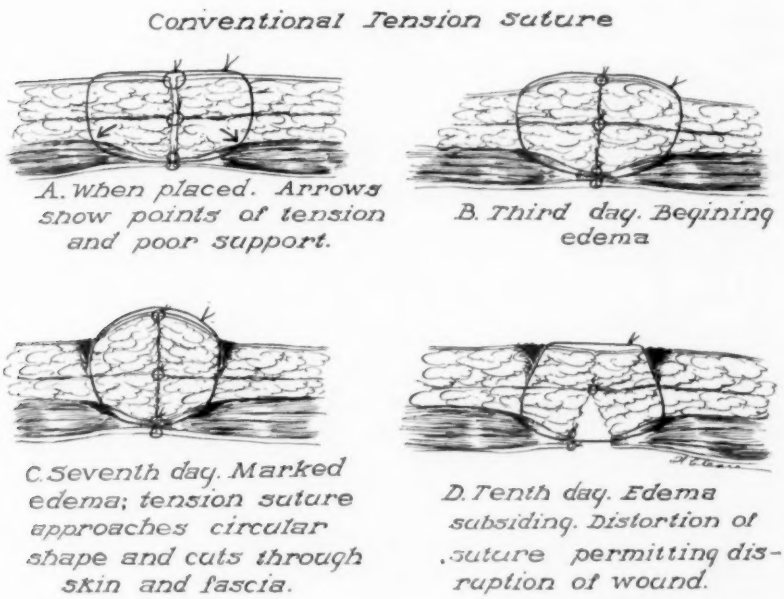
Conventional Tension Suture
A. When placed. Arrows show points of tension and poor support.
B. Third day. Begining edema
C. Seventh day. Marked edema; tension suture approaches circular shape and cuts through skin and fascia.
D. Tenth day. Edema subsiding. Distortion of suture permitting disruption of wound.

FIG. 14.—Drawings made from autopsy material showing the mechanical inefficiency of "stay" sutures commonly used to reinforce abdominal incisions.

intestinal wall is rather easily torn by sutures unless the thread has taken a bite of the tough fibrous submucosa. The second variable factor is the health of the tissues. With acute inflammation tissues become friable; with ischemia—we all tie our sutures too tightly—and with necrosis, tissues slowly give way before the advancing pressure of the thread and we say that the suture "cuts through." The third variable factor is the size of the suture material. The finer the thread, the more readily it will cut through either healthy or diseased tissue. Recently steel wire sutures have become popular; yet steel wire cuts through most soft tissues long before full advantage can be taken of its enormous tensile strength.

Technically, *strain* means distortion due to stress. An example of strain is provided by the conventional tension suture often used in closing abdominal

incisions. Figure 14 shows why that suture is inefficient mechanically and often fails in its purpose because of distortion. The lateral pull of the musculofascial layer is opposed only indirectly by the suture, much as a bowstring opposes the pull of an archer's fingers. Inevitable edema plays its nefarious role.

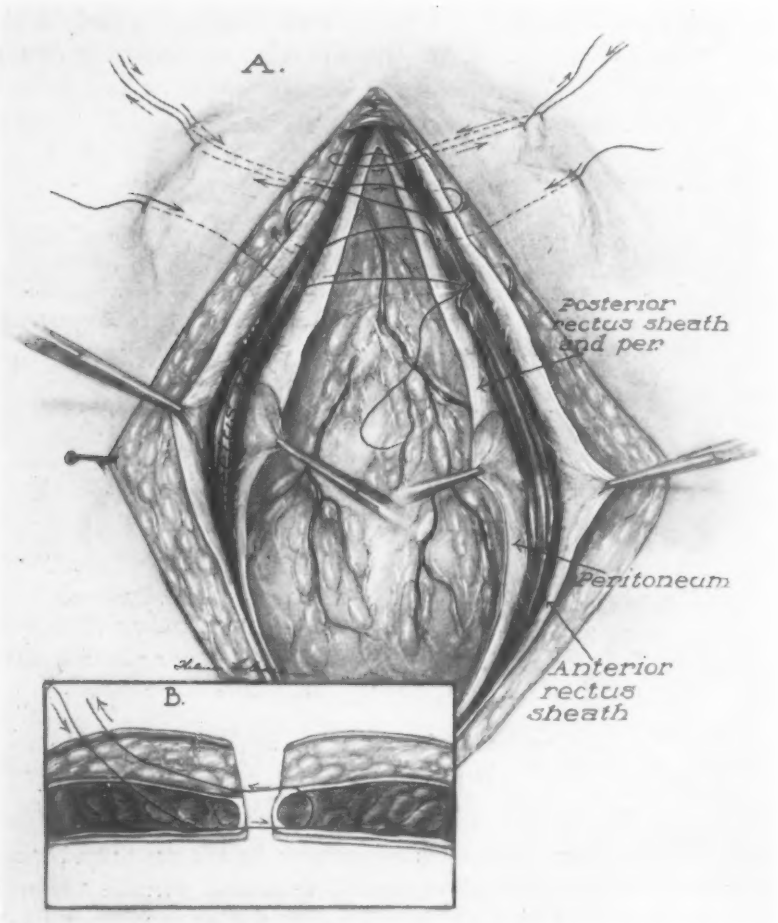

FIG. 15.—A new tension suture which enters the abdominal wall at a distance from the incision, crosses the incision to take a generous bite in the musculofascial layers of the opposite wall, and returns to emerge near the point of entry. The posterior rectus fascia should be grasped by this suture.

Figures 15, 16 and 17 illustrate a tension suture which has been used by the writer during the last two years with satisfaction. There are no closed loops to produce ischemia or to be affected by edema. These sutures, which are staggered, take generous bites of fascia and muscle so as to

minimize the danger of tearing or cutting through. They should be drawn just tight enough to approximate the muscles and fascia. Inasmuch as their pull directly opposes the strong lateral pull of those structures, they cannot be distorted to any extent, unless they break, however great the tension. These sutures can be adapted to paramedian, transverse, subcostal, hockey-

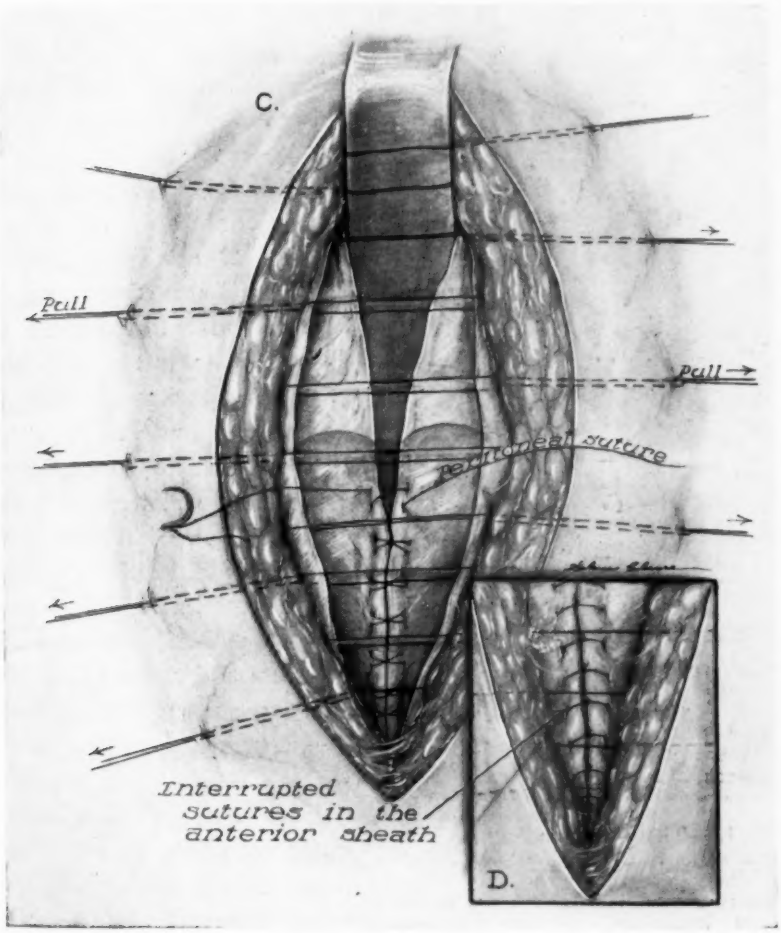

FIG. 16.—Further steps in placing the tension sutures and in closing the abdominal wall.

stick, and T-incisions. If desired, the ends may be tied over rubber tubes or rolls of gauze instead of the metal frame shown in Figure 17. The suture is readily removed after cutting one of the strands close to the skin.

If No. 2 or No. 3 silk or nylon is used, the combined holding strength of these tension sutures is very great, amounting altogether to some 200 or 300 pounds. Patients find them relatively comfortable since they do not tend to cut through or irritate the skin, since their firm support relieves

much of the pain of turning, coughing, and early ambulation, and since they obviate the necessity for tight adhesive strapping and supportive binders.

SUMMARY

No reputable engineer attempts to construct a bridge without knowing first the stresses and strains to which his structure probably will be subjected, the tensile and shearing strengths of his building materials, the calculated total strength of his design, and the margins of safety to be allowed. But in surgery, where the health or life of a patient may literally "hang by a thread," the caliber and sort of suture and ligature material to be used is too often left to guess or habit; the size and spacing of sutures, the number of rows to be used, the sort of knots to be employed, are often simply matters of hand-me-down custom, with scant reference to well-established laws of mechanical forces. Indeed, most surgeons have vague ideas about the amounts of stress and strain which lines of suture are apt to feel, or how best to meet those potential disrupting forces. To play safe, suture material is often used that is unnecessarily coarse, or wire that is many times stronger than the tissues being approximated, or tension sutures that are mechanically inefficient.

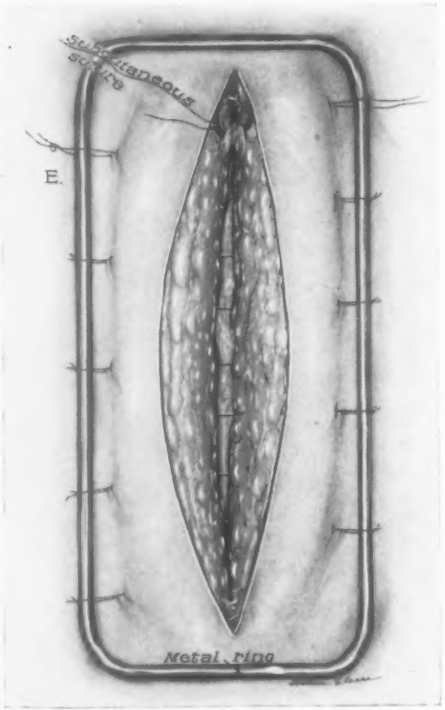

FIG. 17.—These tension sutures are staggered so as to avoid undue squeezing and ischemia of tissues. They are carefully adjusted and tied before the more superficial layers of the wound are closed.

The present paper attempts to explore that neglected but important aspect of operative surgery. Largely on the basis of some original investigations, it presents certain basic principles which should be followed, and offers some practical suggestions which (it is hoped) will give the surgeon better-founded confidence in his ligatures, anastomoses, and wound closures. A new tension suture is described, which is believed to be mechanically superior to the conventional through-and-through tension suture.

Discussion.—Dr. Allen O. Whipple, New York: This subject is one that should be called to the special attention of our residents in training. I believe it is one that is too often neglected in the training of residents. To me this subject has always been of great interest and I have followed some of the earlier writings, particularly the subject of wound repair by Halstead, with extreme interest, and have found that his philosophy has held true throughout. He made certain statements without going into the details, trusting, I believe, to his teaching of his residents and to their own observations—and to me these have always been sound. One was that there was no point in using suture material that was more than twice as strong as the tissues in which the sutures were placed. Second, that non-absorbable suture material and catgut should not be used in the same tissues. The point that Dr. Price has brought out about the importance of eliminating tension on the suture line is something that should be emphasized over and over again. It is studies such as Dr. Price has presented that give real thought and real value to the training of residents, and I noticed in discussing this subject with a group of them recently that they took more interest in that than in almost any other subject. Unfortunately, Dr. Price had to present this material in rather rapid fashion, but I am sure that when we read his paper we will find sound philosophy in it.

FURTHER STUDIES ON THE CYTOLOGIC METHOD IN THE PROBLEM OF GASTRIC CANCER* †

HOWARD ULFELDER, M.D., RUTH M. GRAHAM, B.S.,
AND
JOE V. MEIGS, M.D.

FROM THE VINCENT MEMORIAL LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL

TWO YEARS AGO IN THIS LABORATORY cytologic study was made of the fasting gastric contents of 50 patients suspected of having cancer of the stomach[1]. It was learned that preparations with satisfactory cellular detail were usually possible, and that both benign and malignant cells from the gastric mucosa could be recognized. At operation 24 patients in this series proved to have carcinoma of the stomach; and a correct preoperative cytologic report had been made in 15. One additional cytologic report of cancer was rendered in a patient who showed a benign gastric ulcer after pathologic study. We were particularly impressed by finding malignant cells in two very small cancers, one of them non-invasive (carcinoma-in-situ).

In planning a more detailed study of this technic, particular emphasis has been placed on the method of collecting fluid which is most likely to secure and preserve a cellular specimen representative of all areas of the stomach. Several facts make this more difficult than is the case with most other fluids. One is the rapid action of the digestive ferments present; another is the constant tendency of the intestinal current to sweep material out of reach of the tube, particularly in the case of lesions in the distal segment of the stomach.

METHODS

Both Rehfuss and Levine tubes have been used, in some instances with fluoroscopic check on their position. In a number of patients the undiluted fasting content of the stomach has been examined; others have been allowed to drink water as the tube was passed. After evacuation of the stomach we have irrigated it with saline, with 7% alcohol, or with a 5% suspension of clove oil. The secretion stimulated by parenteral injection of histamine has been examined in the majority of cases. Repeated study with varying techniques has been possible in a few instances.

Out of these observations a standard procedure has been evolved. A number of additional openings are made in a size 14 Levine tube. It is introduced through the nostril in the usual manner for a distance of 75 centimetres; the patient is allowed to drink tap water to facilitate this maneuver. The stomach is then evacuated as completely as possible. This is our first specimen. One hundred cubic centimetres of normal saline is injected, the

* This study was supported by a grant from the American Cancer Society.

† Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

tube is clamped, and the patient lies first on one side, then on the other, then on his face, and finally sits up or walks. The saline is partially withdrawn and reinjected several times during this procedure. Finally the stomach is again aspirated until empty. Both samples of fluid are centrifuged immediately for 20 minutes at about 2000 r.p.m., the supernatant fluid poured off, and thin smears made from the sediment. These are fixed and stained by Papanicolaou's method[2].

RESULTS

To date, 48 patients have been studied in this fashion. The specimens were unsatisfactory in three, all of whom had obstruction and an appreciable degree of gastric retention. At operation two had benign ulcers and one had carcinoma.

Eminently satisfactory cellular preparations were secured in the remaining 45 cases. Operation has disclosed carcinoma of the stomach in 14, 12 were diagnosed correctly by our method. One other report of malignancy has been rendered in a patient with no detectable gastric lesion and in whom no operation has been performed. One patient proved to have malignant lymphoma of the stomach. The cytologic preparation in this instance contained no abnormal cells of any type.

SUMMARY

Various methods of preparing cytologic specimens from gastric fluid have been studied and a standard procedure evolved. Satisfactory cellular detail has been noted in all cases except those where appreciable obstruction exists. The accuracy of this method of diagnosis in our hands has increased since the introduction of the modifications described herein.

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[2] Papanicolaou, G. N.: New Procedure for Staining Vaginal Smears, Science, **95**: 438-439, 1942.

DISCUSSION.—DR. JOE V. MEIGS, Boston (closing): We feel that the diagnostic method presented by Dr. Ulfelder is perhaps a partial answer to the many times I have listened to surgeons present the tragic results of surgery for carcinoma of the stomach. I have heard presentations of a hundred patients operated upon and at the end of five years only a few were alive. If by this method we can find even only one early carcinoma—and we have found more—its value is proven. We believe it is better sometimes than x-ray examination, better sometimes than gastroscopic examination. We may be able to pick up cases that have a chance for cure. It is a very fussy business and it needs an expert. Recently Mrs. Graham in our Vincent Hospital Laboratory has told me that within the last eighteen months any patient that she said had a positive smear for carcinoma of the cervix had carcinoma of the cervix. She has picked up between 25 and 30 unsuspected cancers of the cervix. It is wrong for us to think that as clinicians we can do this work. It should be done by experts. At a recent meeting in Boston, under the auspices of the American Cancer Society, it was generally recognized by the pathologists that it was their duty to teach this method

of diagnosis to their residents, so as to spread the proper means of technic throughout the country. The best cytologists can make mistakes. It seems to me it is essential that we have under tutelage and instruction a goodly number of men who will be experts in making cytologic diagnoses. I believe earlier diagnosis can be made through this method than by any other we have at present.

ANTERIOR RESECTION FOR MALIGNANT LESIONS OF THE UPPER PART OF THE RECTUM AND LOWER PART OF THE SIGMOID*†

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THE OPERATION OF ANTERIOR resection for lesions of the terminal part of the large intestine with re-establishment of intestinal continuity has been criticized by many authors as not being sufficiently radical. The present paper is an evaluation of the operation. The efficacy of any surgical procedure for cancer is judged by the number of persons undergoing the procedure who are alive five years or more and not on an anatomic basis —the extent of the excision.

This study is limited to the most controversial segment of the large intestine; namely, the distal 20 cm. It is for this region that new procedures are constantly being advocated and interest in old ones is being rekindled. A matter of 3 or 4 cm. from the dentate line makes the difference between an operation involving a permanent colonic stoma and one in which intestinal continuity can be re-established. While the majority of patients become adjusted to a permanent colonic stoma, there are some who have difficulty in its management. It should be remembered that those "cured" by anterior resection can live normally in every respect.

Because it is so important in determining the possibility of re-establishing intestinal continuity, I have considered the cases in this study in respect to the distance of the lower edge of the lesion from the dentate (pectinate) line as measured by the proctoscope. By studying the prognosis for each segment separately one could determine the lowest level at which it is sage to apply the procedure. I have avoided the use of the term "rectosigmoid" since it is merely a clinical designation for the rectosigmoidal juncture. Variation of the length of the rectum and of the level of the pelvic peritoneal fold, change of the length of the rectum after mobilization, shrinkage of the tissue by the time the pathologist measures it and differences in the interpretation of descriptive terms have led me to depend on the distance measured proctoscopically.

DEVELOPMENTAL BACKGROUND

The operation of anterior resection had been applied to lesions of the sigmoid before 1910, at which time primary anastomoses were performed, a large rectal tube being placed through the anastomosis for the purpose

*Read before the American Surgical Association, Quebec, Canada, May 27, 1948.
†I am indebted to Dr. A. L. Lichtman and Dr. G. Lowe for some of the material used in preparation of this paper.

of decompression. The application of the procedure to lesions of the rectum came about in a roundabout way. A series of operations were performed in which continuity of the bowel was not re-established. In the first stage sigmoidal loop colostomy was performed; in the second procedure the lesion and its mesentery were excised and the sigmoidal and rectal stumps were closed. If the patient survived, subsequent exploration and re-establishment of intestinal continuity were warranted. It became customary to advise the patients that if they got along well they could return in six to 12 months for sigmoidorectostomy. The satisfactory survival rates, despite extensive lesions of high grade, suggested that the intestinal anastomosis could be performed at the second stage of the operation. Three facts were apparent: First, the rectal stump can survive if supplied by the inferior hemorrhoidal vessels alone, regardless of the fact that the textbooks have denied this; secondly, Sudeck's point is not as critical as described and, thirdly, it is possible to excise sufficient tissue in the mesocolon and distal portion of the sigmoid and to obtain good clinical results. Apparently it sufficed to remove only 3 or 4 cm. of bowel distal to the lesion. This latter observation was difficult to reconcile with Miles's[9] work but subsequent careful study of cleared specimens showed that the occasional distal spread of carcinoma to lymph nodes beyond 2 cm. is due to proximal blockage.[1,7,13] In such instances it is possible that no surgical procedure is sufficiently radical to include the centrifugal spread from such obstructed lymphatic drainage.

The procedure outlined here I first performed in 1930. It has been reported previously in detail.[2-4] Up to 1938 the majority of such operations were carried out in three stages including preliminary transverse colostomy. In the second stage the lesion was removed and colosigmoidostomy or colorectostomy was performed through a low left rectus incision. In the third step the colonic stoma was closed after suitable clamping of the spur. Since 1938 colostomy has been performed at the time of resection unless there was severe obstruction. With progress in methods of decompression and with the preoperative use of sulfasuxidine or sulfathaladine and vitamin K, antecedent colostomy is being performed in fewer cases than before. At present, with few exceptions, patients come to the operating room well prepared by administration of sulfasuxidine and rectal irrigations, and the surgeon has definite proctoscopic information regarding the grade, level, mobility and extent of the lesion. This has reduced the mortality rate and permitted the performance of an open accurate anastomosis.

The performance of sigmoidal colostomy as a preliminary or emergency procedure in these cases makes the resection extremely difficult by limiting the mobility of the colon and frequently dissection of the colonic stoma from the abdominal wall is necessary in addition to the performance of transverse colostomy.

Since 1941 such patients have received preoperatively a minimal daily oral administration of 12 Gm. (180 grs.) of sulfasuxidine or sulfathaladine

for a period of three to eight days. In addition, 5 Gm. of sulfathiazole is scattered intraperitoneally at the close of the operation. I feel that this chemotherapy has produced a distinct reduction of the mortality rate. Culture of stools after adequate preparation with the insoluble, poorly absorbed sulfonamides has shown a dramatic fall of the count of coliform organisms. This advantage is appreciated most by the surgeon who prefers an open anastomosis. With the use of the sulfonamides, peritonitis has become much less common. In addition, there has been a fall in the incidence of thrombophlebitis and pulmonary emboli, probably resulting from a reduction of the contribution that is made by infection in these complications.

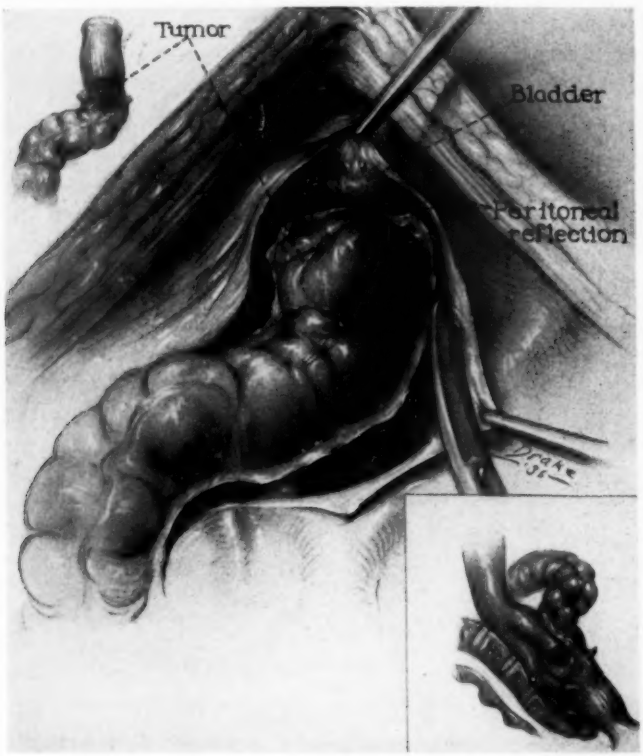


FIG. 1.—The peritoneum is incised as indicated, freeing the sigmoid and rectum. The rectum is mobilized from the sacrum as shown in the lower right insert.

The use of streptomycin was for a time thought to be as effective in reducing the coliform count as was that of either of the aforementioned sulfonamides. It has been demonstrated that streptomycin does lower the bacterial count in the bowel but for two to three days only. After this period, regardless of the amount of streptomycin administered, the coliform organisms return to their normal count. It would seem, therefore, that streptomycin must be considered as an adjunct only to sulfonamides in surgery of the colon.

THE TECHNIC OF LOW ANTERIOR RESECTION

The operation is performed with the patient in a steep Trendelenburg position and a long left rectus muscle-splitting incision is used. The pelvic colon is mobilized by dissecting the fused lateral peritoneum free from the mesosigmoid. The peritoneal incision is outlined so that an adequate cuff of peritoneum is excised with the colon, passing up the lateral aspect, curving around the rectovesical or rectocervical space and passing back on the mesial aspect (Fig. 1). The entire left portion of the colon is then mobilized by incising the lateral peritoneal reflection of the left paracolic gutter as far as the splenic flexure. Both ureters are identified and isolated.

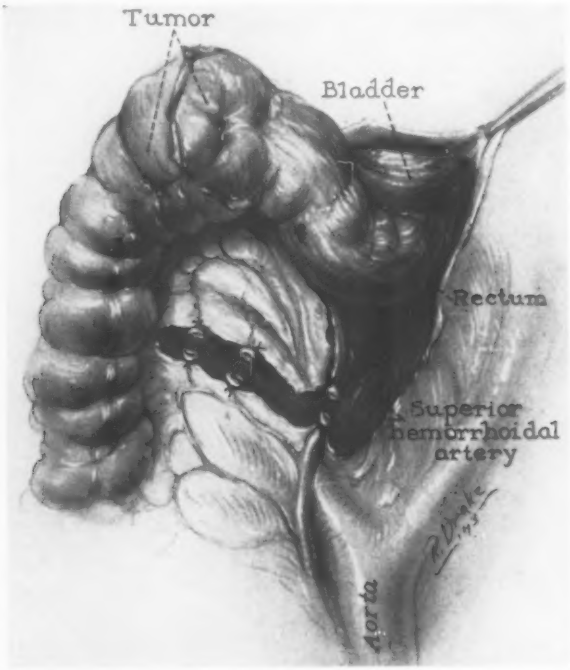


FIG. 2.—After mobilization of rectum and sigmoid the site for the ligation of the superior hemorrhoidal or inferior mesenteric vessels is selected and a V-shaped section of mesentery is excised.

The rectal ampulla is then mobilized from the hollow of the sacrum as far as the coccyx (Fig. 1) and from the vagina or seminal vesicles and prostate by blunt and sharp dissection. Usually in the case of a low lesion, such as is under consideration here, a large portion of the branches of the middle hemorrhoidal vessels, which are of irregular distribution, must be sacrificed.

The mobilized mesocolon is then transilluminated and the vascular pattern is determined. When the mesentery is very fat one must depend on palpation. The point of ligation of the inferior mesenteric or superior hem-

orrhoidal vessels is then outlined. My colleagues and I do not recognize any critical point in this determination, rather depending on the precepts of rational cancer surgery and providing the correct amount of excision to allow the sigmoid or descending colon, as the case may be, to reach or bridge to the rectal or rectosigmoidal transection without tension. It should be recognized that the mesentery of the sigmoid usually is omegoid and that one obtains more colon to reach into the pelvic outlet by going higher up with the mesenteric ligation (Fig. 2). Because of this the low resections themselves insure the adequate resection of the pelvic mesocolon since often it is impossible to obtain enough mobile colon unless one ligates rather high up on the inferior mesenteric artery. While in the earlier developmental years, resections were somewhat less radical, there has been a tendency in the past five years to standardize the operation more or less so that as much bowel as possible is removed even if the lesion is situated above the pelvic peritoneal fold.

If one does not feel certain of the pattern of the circulation to the upper segment, the bowel may be transected before the inferior mesenteric artery is ligated and the effect of ligation at the selected site may be determined by pinching the artery. Instead of depending on the color of the intestine it seems wiser to look for the pulsations in the arteries as they enter the colonic wall. After ligation of the vessels and transection of the colon the intestine is reflected over the pubis. Steady slow traction is exerted on the rectum with a hand deep in the hollow of the sacrum. The smooth muscle of the rectum and vascular stalks relaxes slowly. The curves, valves and folds of the rectum straighten and give more length. The anal canal and levator ani muscle are slowly funneled into the pelvic bowel. This maneuver may permit ligation of the rectal stalks as far lateral as 4 cm. to include any lateral spread in this area. These measures permit placement of rubber-covered intestinal clamps (Fig. 3) well below the lesion in selected cases even when it is 6 to 8 cm. from the dentate line. Actually, after mobilization of the rectum, the lesion is 10 to 12 cm. from the dentate line and one can resect the normal rectum at least 3 to 4 cm. below the lesion. In order to determine completeness of resection, frozen sections of the distal portion of the resected rectum are made routinely and thus a check is made on the surgeon's ability to palpate the lowest limit of spread.

The colon is then prepared for anastomosis to the rectum by placing another especially constructed rubber-shod curved intestinal clamp close to the end. The fat must not be cleared from the edge too extensively or the blood supply which enters the colon through the base of the fat tags will be sacrificed. The curved clamps on the colon and the curved clamps on the rectum are placed side-by-side (Fig. 3) in the deep pelvis and an open end-to-end anastomosis is performed without tension. Since the posterior portion of the rectum is thin and devoid of serosa only a single posterior row of stitches is placed. Anteriorly the rectum is thicker and a second

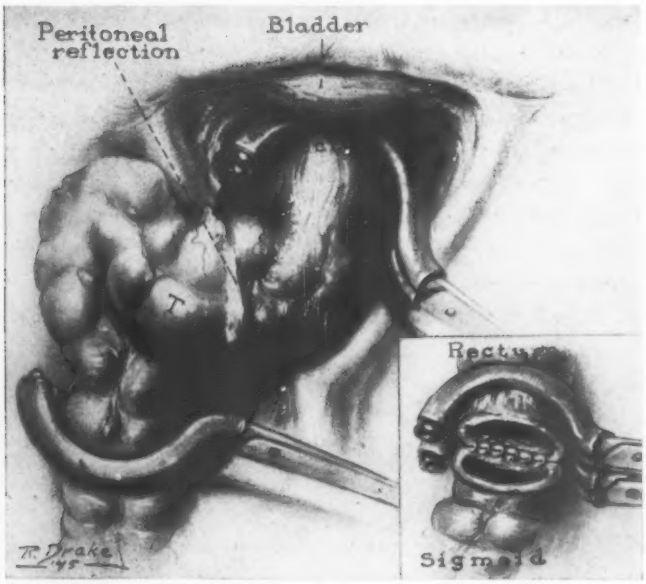


FIG. 3.—Curved intestinal clamps are placed beyond the lines of resection of the intestine. After the segment is resected the clamps are placed side by side and the open colorectostomy is performed as indicated in the insert.

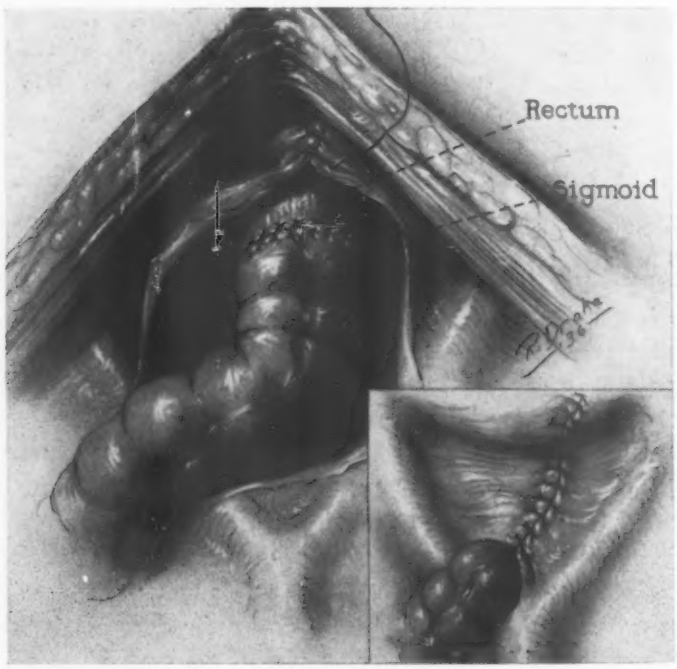


FIG. 4.—The pelvic peritoneum is closed at a higher level, which makes the anastomosis retroperitoneal. The drain has been omitted from the drawing.

inverting row is feasible. Any so-called aseptic anastomosis in this region is a gymnastic feat attended by difficult clamp maneuvers deep in the pelvis, danger of tearing the rectum, the hazard of catching the opposite mucosa to create a persistent diaphragm or of perforating the rectum in forcing the anastomosis open, and finally the possibility of a poor anastomosis. A valuable extra centimeter or more of rectum may be consumed in the process. Furthermore the posterior rectal wall is so thin that every stitch passes into the lumen and occasionally tears the rectal wall. For these reasons one questions how aseptic the closed anastomosis is.

In concluding the operation, 5 Gm. of sulfathiazole is dusted into the region of the anastomosis, a Penrose cigaret drain is placed in the hollow of the sacrum, emerging through the lower angle of the incision, and the peritoneum is sutured around the colon to reconstruct the pelvic floor proximal to the anastomosis (Fig. 4). The incision is closed after a loop of the transverse colon has been brought through the omentum and out of the upper angle of the incision to serve as a temporary colonic stoma and the omentum is brought down to cover the loops of intestine.

In the early cases the drain was brought out through an incision just in front of the coccyx. While the drainage is excellent, this introduces difficulties in draping the patient so that the assistant can make the stab wound to draw the drain through. Furthermore, the site of drainage is uncomfortable to the patient and it is easily contaminated and favors temporary fistula at the site. My colleagues and I have found that a drain brought out suprapubically is satisfactory and usually we begin to remove it about the eighth postoperative day. In cases in which there has been considerable perforation or soiling, sulfadiazine is administered postoperatively. Otherwise it is not necessary unless some abdominal or pulmonary complication indicates its use. Sulfasuxidine is administered only when a fistula or leak presents. When proximal colostomy is performed, a paste of sulfasuxidine can be instilled into the distal loop. The colonic stoma is opened by cautery incision in the patient's room from 18 to 24 hours after operation.

The colonic stoma usually is closed three to four weeks after the anterior resection. In preparation for the closure, patency and healing of the anastomosis are tested by passing water downward from the distal loop of the colonic stoma and upward from the anus. If a proctoscopic examination is made in the interval before closure the anastomosis is occasionally found to be as small as 2 cm. in diameter. A proctoscopist who has not encountered similar cases before will be distressed over the finding and will occasionally advise against the closure of the colonic stoma because of stricture. However, it has been found that although the lumen at the site of anastomosis may appear small the function is satisfactory and proctoscopy no longer is performed on such patients before closure of the colonic stoma. The free passage of water up and down through the anastomosis

is accepted as adequate proof of satisfactory function. Normally, the rectosigmoidal junction is the narrowest part of the colon and such narrowing is consistent with normal function. The subsequent passage of fecal matter is the best dilator and at a later time the anastomosis will be found to be much larger than before. Delay in closure will only serve to permit further narrowing because of disuse and scar formation (contraction).

Leakage from the site of anastomosis occurred in 12 cases but with the proximal temporary colonic stoma, there is little febrile reaction and there is merely a delay of an extra week or two for the fistula to close before proceeding with closure of the stoma.

The preoperative preparation employing sulfasuxidine and the technic of closure of the colonic stoma were reported in 1944.[5] That report presented data on 102 cases in which colonic stomas made in various surgical procedures were closed by a standardized intraperitoneal procedure without a single death. Since then, the closure of colonic stomas has been performed with two deaths. The mortality rate for the entire series of closures is 0.6 per cent. In the deaths mentioned, one was caused by coronary occlusion. The patient had suffered from angina for five years. The cause of the second death was probably peritonitis. Necropsy was not permitted. A fecal fistula developed in three cases. In three cases there was purulent drainage and escape of gas. Five of the fistulas closed spontaneously within two months. In the remaining case the escape of gas occurred intermittently for ten months and then the fistula closed spontaneously. This would appear to demonstrate that the added risk of temporary colostomy is small if full advantage is taken of chemotherapy before and during closure of the stoma.

During the past five years, postoperative roentgen therapy has been used as an adjunct to surgical treatment in a series of patients whose lesions had progressed to the state of nodal involvement. An impression that this may be of value has been obtained from sporadic cases in which it was tried. The consensus at present seems to be that roentgen treatment is of little or of no value. Definite information on this matter will not be available for some time.

The question of provision of a temporary colonic stoma.—Previous to the advent of the sulfonamides, numerous methods of decompressing the colon proximal to the colorectal anastomosis were investigated but the provision of a temporary defunctioning loop type of transverse colonic stoma proved apparently to be the safest procedure. Enterostomy, appendicostomy and cecostomy were less efficient. A rectal tube with its orifice proximal to the anastomosis occasionally was responsible for ulceration and perforation of the colon and frequently became plugged. Preliminary sigmoidal colostomy has many disadvantages, which have been outlined earlier in this paper. The advent of sulfasuxidine warranted re-evaluation of the safety of omitting colostomy. The problem was approached with an open

mind but, at present, the mortality rate is considerably higher when colostomy is omitted than when it is included. The possibility exists that the introduction of coliform-effective antibiotics may make anastomosis without proximal colostomy safe if the lesion is above the pelvic peritoneal fold. Analysis of recent series of cases of anterior resection without colostomy[8,11,12] reveals that many of the lesions were above the pelvic peritoneal fold; yet in 10 to 20 per cent of the cases colostomy had to be performed as a postoperative emergency operation.

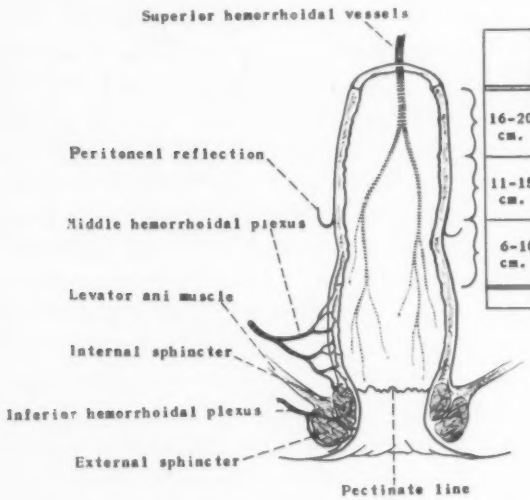
The omission of temporary colostomy in cases in which the lesion is near or below the pelvic peritoneal fold is fundamentally dangerous because the blood supply to the distal segment has been decreased. The sigmoidal anastomotic vessels above and the inferior hemorrhoidal vessels below provide a marginal blood supply that is adequate for healing under ideal conditions but not under strain. It has been long realized that anastomosis of a serosa-covered segment of bowel to a segment devoid of serosa requires 14 to 21 days to heal completely. Pemberton[10] has recently demonstrated by means of roentgenographic study of the segment of bowel distal to the colonic stoma in cases of low anterior resection of the lower part of the sigmoid and of the upper part of the rectum that at the site of the anastomosis barium often leaks into the pelvis or the hollow of the sacrum. Such leakage must then occur in many cases in which a colonic stoma is not established. Proximal colostomy seems indicated also if the lesion is adherent to the posterior vaginal wall, for the branches of the middle hemorrhoidal artery which supply the vaginal wall are often sacrificed in the dissection. Rectovaginal fistula may develop in such cases, especially if a temporary colostomy is performed. Closure of the stoma is then deferred for a month or two; this is occasionally necessary for complete healing in cases in which a portion of the vaginal wall has been excised.

I have applied the technic outlined in this paper in 523 cases, the first operations having been performed in 1930. In 46 cases, even though the distal loop was long enough to permit exteriorization, a short mesentery, obesity, intussusception of the growth, or some anatomic variation made anterior resection the procedure of choice. In 477 cases the lesion was 20 cm. or less from the dentate line. Of these operations, 39 were palliative and the procedure was performed in the face of distinct nodular metastasis to the liver. A number of these patients lived for more than a year. The lesion had invaded the wall of the bladder extensively in 12 of the cases and simultaneous partial cystectomy was performed. The latter group of cases was included in a recent report.[6]

Age.—The average age of the patients was 53.8 years. The youngest patient was 7 years of age and it is gratifying to report that this boy is still alive seven years after operation. Two of the patients were 79 years old.

Sex.—Of the 426 patients 55.6 per cent were male and 44.4 per cent were female. However, if the cases are analyzed it can be seen that the

worst lesions are found among females. Thus, in 24 of 37 cases in which there were high-grade malignant processes with nodal involvement the patients were female. In 28 of 40 cases in which the patients were less than 36 years of age, the patients were female. If one examines the lesions between 6 and 10 cm. one will find that the male to female ratio is 40:60. As the level proceeds toward the dentate line the proportion of females increases and the grade of the process rises, as has also been noted when one approaches the dentate line from below. To summarize: The lesions among females tend to be of higher grade and closer to the dentate line than among males, while the patient tends to be younger.



	Grade	Nodal involvement Without	With	Cases	Total cases
16-20 cm.	1	22	9	31	118
	2	45	28	73	
	3	4	8	12	
	4	0	2	2	
11-15 cm.	1	21	8	29	132
	2	44	41	85	
	3	9	5	14	
	4	2	2	4	
6-10 cm.	1	8	8	16	90
	2	16	24	40	
	3	11	13	24	
	4	3	7	10	
					340

FIG. 5.—Distribution of the malignant lesions in the 340 cases in which the operation of anterior resection was applied. Palliative operations are omitted. The number at each stated distance from the pectinate (dentate) line is given in the figure. The incidence of each grade with and without nodal involvement is also included.

Pathologic character and location of lesions.—The lesions in the 426 cases were all adenocarcinomas. Figure 5 shows the distribution by grade and nodal involvement for each 5 cm. segment in the region under consideration. The specimens were not cleared but were examined by multiple incisions in the search for lymph nodes. All of the lesions were segregated according to Dukes's classification and graded by Broders' method. Few lesions of type A were found in the series. The majority of the lesions removed by anterior resection were perforating, since the rectum is so thin that all layers are usually involved before detection. Twenty lesions (5.9 per cent) were of the mucous (colloid) type. Five were described as papillary. Multiple synchronous malignant lesions were found in 18 cases (5.3 per cent). Gross venous or perineural involvement, which invariably gives a poor prognosis, was noted in seven cases.

The lesions were separated into groups depending on their distance

from the pectinate line (Fig. 5). This was done in order to learn if there was a difference between the survival rates of patients having lesions at various levels in the bowel, for if the operation of anterior resection is not sufficiently radical the survival rate of those having the lowest lesions would certainly be less than that of those found to have lesions above the pelvic peritoneal fold.

Resectability, indications and limitations of the method.—The examination of any large series of cases in which there are lesions in this zone shows that 12 to 14 per cent of the patients have gross hepatic, peritoneal or omental involvement and that only palliative colostomy is justifiable. In the series being reported resection was undertaken even when the palpable hepatic nodules aggregated less than 3 cm. in diameter.

The resectability of the lesions by the method of anterior resection depends on the level of the lesion. For lesions more than 10 cm. from the dentate line the resectability rate was 86 per cent. All resectable lesions at this level were removed by anterior resection. If the lesion was perforating, a part of the abdominal wall or psoas muscles was excised by cautery as necessary. Involvement of the bladder, ureters or small intestine did not prevent resection. For lesions at 10 cm. from the dentate line the resectability rate was 80 per cent and for those at 8 cm. it was 44 per cent. This is the lowest level of general applicability of the operation. At 6 cm. there must be favorable anatomic relations—a thin person with a broad, flat pelvis. It is my opinion that low anterior resection is applicable only rarely when the lesion is situated as low as 6 cm. from the dentate line. There are several alternative methods for handling such lesions. In this region one approaches the point where the allowable 3 cm. of retrograde spread and lateral direct extension involve the lateral efferent lymphatics accompanying the middle hemorrhoidal vessels. Such lesions must be resected by a method which in addition to removing the spread in the pelvic mesocolon allows for resection of (1) the stalks of the middle hemorrhoidal vessels, (2) levator ani muscle with the nodes included between it and the pelvic fascia, (3) the ischiorectal fat and (4) a large part of the perianal skin. One must not apply the pessimistic aphorism that if the lymphatics or veins are involved no operation is radical enough and that if there is no spread of the disease most operations for cancer are too radical.

HOSPITAL MORTALITY RATE FOLLOWING ANTERIOR RESECTION

In the 426 cases of anterior resection of lesions between 6 and 20 cm. from the dentate line there were 25 deaths (5.9 per cent). Eighteen of the deaths occurred after the first stage of the operation, the anterior resection, and seven followed closure of the colonic stoma. Seven of the 18 deaths after anterior resection followed peritonitis, two followed pelvic abscess, and each of the following was responsible for a death: coronary occlusion, pulmonary embolus, diabetic acidosis and bronchopneumonia. Of the seven deaths following closure of a colonic stoma, four resulted from peritonitis,

two from pulmonary embolus and one from coronary occlusion. Five of the seven deaths occurred before antibiotics and sulfonamides were employed preoperatively and postoperatively.

The mortality rate from colonic operations has fallen remarkably with the years. For all operations on the colon at the Mayo Clinic in 1934 the mortality rate was 16 per cent. For some reason the rate increased in 1936 and was 22 per cent but during the past four years it has been less than 5 per cent. I attribute a large part of the success in reducing the mortality rate to the use of sulfonamides. Inspection of the figures broken down, to reveal the rates for the sigmoid, rectosigmoid and rectum, will further demonstrate this. From 1907 to 1936 the mortality rates remained nearly constant and those figures are grouped together. The startling improvement

TABLE I.—*Anterior resection* 1930-1947: *hospital deaths by periods*

Date	Cases	Deaths	
		Number	Per cent
1930-1935	47	4	8.5
1936-1940	109	14	12.8
1941-1947	270	7	2.6
All years	426	25	5.9

TABLE II.—*Anterior resection; nonpalliative operations; five-year survival rates for different levels*

Distance from dentate line, cm.	All cases		Nodes not involved		Nodes involved	
	Number	Per cent survival	Cases	Per cent survival	Cases	Per cent survival
6-10	74	63.7	32	72.4	42	57.1
11-15	97	70.2	58	78.8	39	57.7
16-20	101	66.9	60	71.5	41	60.4
All levels	272	67.7	150	74.0	122	58.5

has occurred in the resection of sigmoidal lesions. The mortality rate following sigmoidal resection is 8.2 per cent of what it was ten years ago while that of the rectosigmoid is 15 per cent, and of the rectum, 41 per cent of what it was ten years ago. Resection of the rectum which used to be the safest has been improved the least and now operation in that region is carried out with the least safety. The majority of operations for lesions in this segment are combined abdominoperineal procedures. The improvement in rectal surgery occurred at the time of the introduction of the intraperitoneal vaccine and systemic and intraperitoneal administration of sulfonamides. There was no additional improvement from the use of sulfasuxidine. On the other hand, with lesions occurring above the pelvic peritoneal fold, there was a further marked improvement after the introduction of sulfasuxidine. The improved results cannot alone be attributed to vitamins, intravenously administered amino acids, multiple blood transfusions or aseptic anastomosis, since these adjuvants were rarely used in this series of cases.

Table I shows the mortality rates for the operation of anterior resection for three periods. During the years 1936 to 1940 more tissue was excised at the operations than previously and the mortality rate was 12.8 per cent. This mortality rate compares favorably with that for other operations in the same region at the same period. However, in the past seven years, the mortality rate has been reduced to 2.6 per cent.

SURVIVAL RATES

In 272 cases the operation was performed sufficiently long ago to provide data for calculating survival rates. Figure 6 shows graphically the survival rate in the 272 cases. After five years 67.7 per cent of the patients were alive; 49.8 per cent were alive after ten years. By the method of calculating survival rates it is impossible to prolong the curve beyond the last death recorded in the series.

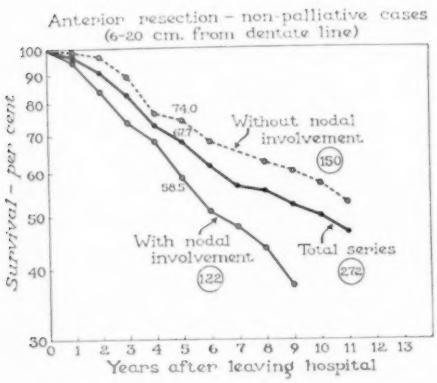


FIG. 6.—Survival rates of 272 cases in which the operation of anterior resection was performed. Palliative operations are omitted. The poorer prognosis in the 122 cases in which the lymph nodes were involved is demonstrated. The five-year survival rates are indicated.

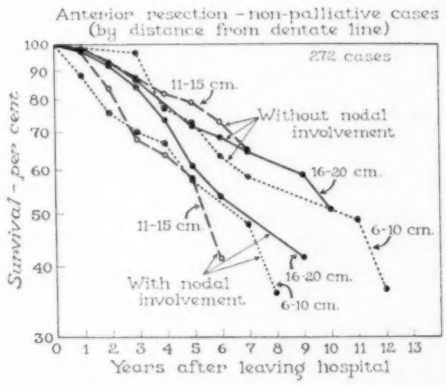


FIG. 7.—Survival rates of the same 272 cases as are included in figure 6. In figure 7, however, the rates are given for the different segments of the rectum and sigmoid in order to show that the operation of anterior resection applied to the upper half of the rectum is not attended by a greater degree of recurrence.

Table II gives the five-year survivals for each level in cases with and without nodal involvement. The best results were obtained from the removal of lesions occurring 11 to 15 cm. from the dentate line. It was hoped to show the effect of the grade of the lesion by breaking down this table but the numbers were too small to be statistically significant. Worthy of mention however are two cases in which the lesion was of grade 4, type C (Dukes). The patients are still alive six years after the resection. The first patient on whom the operation was performed in 1930 is still alive. Figure 7 shows graphically the survival rates for cases with and without nodal involvement divided according to incidence at each level in the bowel. Here again it was necessary to discontinue the curve at the last death in the series.

In 20 of the cases the lesion was of the mucous (colloid) type of adenocarcinoma; 18 patients were dead within three years. One patient lived five years; the other survivor lived nine years. It seems that the mucous type of lesion is rarely amenable to cure by resection. A similar poor prognosis was noted for those cases in which the lesion was of the papillary type, for none of the five patients lived for three years.

In eight cases an asynchronous primary malignant lesion was subsequently removed; in five of these cases the lesions were in the colon and in three they were in the breast. Of the 85 patients who survived operation but died subsequently, the cause of death, according to available data, was obtained either at death, on a return visit to the clinic or from an adequate report from the local physician who was present at the death. In 15 cases there was local recurrence of the disease. In four carcinomatosis was present and in four, intestinal obstruction was responsible for the death. In 20 cases the liver was involved but there was no evidence of local recurrence. Metastasis to the bone was observed in five cases, to the liver and bone in two, and to the lung and bone in two. In 11, the death was from some other cause: cardiac in four, cerebral hemorrhage in three, pneumonia in two, and from an accident in two. The cause of death was not definitely determined in six cases.

Stricture at the site of anastomosis occurred in five cases. This condition was managed by manual dilation in two cases. In two cases exploration was carried out; one required reperformance of colostomy six months after a stoma had been closed. This patient subsequently refused laparotomy to repair the stricture and still depends on the stoma for adequate elimination.

SPHINCTERAL CONTROL AND SEXUAL FUNCTION

No change in sphincteral control was observed in any of the cases. In fact, many patients who formerly complained of constipation stated that their intestinal habit had improved.

Although a survey was not made of the sexual function in cases after operation there seemed to be no complaint, other than that eight male patients volunteered that while erection occurred as before there was no emission during ejaculation. In all of these eight cases the lesion was low in the bowel and extensive and it is probable that the seminal vesicles or ducts were detached in the course of the dissection.

RELATIONSHIP OF ANTERIOR RESECTION TO OTHER PROCEDURES

When it was found at the exploratory operation that the lesion was too low in the bowel to be removed by anterior resection, colostomy was performed and the lesion removed by posterior resection two to three weeks later, with the patient in prone position. If the patient is in good condition or if there is nodal involvement a single-barreled sigmoidal stoma is provided by bringing the bowel out through a stab wound, the superior hemorrhoidal vessels are ligated and the sutured stump of rectosigmoid is left free in the abdomen.

The blood supply from the middle and inferior hemorrhoidal vessels is adequate to sustain the normal intestine but when posterior resection is carried out approximately two weeks after colostomy it is observed that the lesion has undergone degenerative changes and its vessels are thrombosed. If the patient presents a poor risk, double-barreled sigmoidal colostomy is as much as should be attempted at the time of the exploratory procedure. In such circumstances, at perineal resection, one can ligate the vessels and transect the intestine well up in the abdomen. One does not attempt to remove the rectum as a tube but takes out all of the perirectal tissue en bloc, dissecting along the membranous urethra and prostatic capsule, or vaginal wall, as the case may be. The coccyx is removed and the levator ani muscle with its investing fascia and nodes is resected. No procedure really eliminates the lateral spread to the hypogastric nodes but one carries out the most radical excision that is possible.

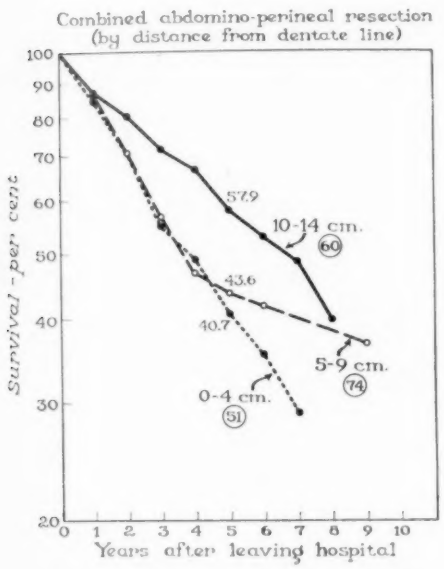


FIG. 8.—Survival rates in 185 cases in which the Miles combined abdominoperineal resection was applied. The incidence in the various segments is given and the curves show the poorer prognosis after resection of lesions of the lower half of the rectum. The five-year survival rate for each segment is indicated.

When performed in the classic fashion[9] the one-stage combined abdominoperineal resection leaves little room for improvement. However, in practice, a poor resection is common in the region of the lesion, while the resection of the pelvic mesocolon is excellent. After spending the major part of the time eliminating the distal spread of the disease the surgeon may merely cone out the rectum itself, ignoring the local lateral efferent lymphatics. A radical abdominal operation and a radical perineal resection are often more than the average patient can withstand at one time.

To evaluate this contention I have selected a group of cases in which one-stage combined abdominoperineal resection was carried out during the same time interval as the anterior resections were performed and have divided the cases according to the distance between the lesion and the dentate line (Fig. 8). The series are not strictly comparable with one another but the differences in survivals for the same operation at different levels are comparable. The five-year survival rate for the patients having the lowest lesions, 0 to 4 cm., was 40.7 per cent; for lesions 5 to 9 cm. from the dentate line it was 43.6 per cent, and for those 10 to 14 cm. from the dentate line,

57.9 per cent. The survival rates in cases in which the lesions were below the pelvic peritoneal fold and in which the combined abdominoperineal resection was employed, are distinctly poorer than those in cases in which the lesion was above the pelvic peritoneal fold. The added incidence of lesions in the lower segment with nodal involvement is not sufficient to account for the difference.

To complete the picture, Figure 9 shows the survival rates in 475 cases of posterior resection performed in the same interval, 1930 to 1944 inclusive. It will be remembered that this operation was carried out when the lesion was too low for anterior resection. Therefore, it includes the most extensive lesions at 6 to 8 cm. from the dentate line in addition to all of the lesions below 6 cm. that were encountered in the series. Thus, the group of anterior resections plus this one of posterior resection corresponds roughly to the group of combined abdominoperineal resections.

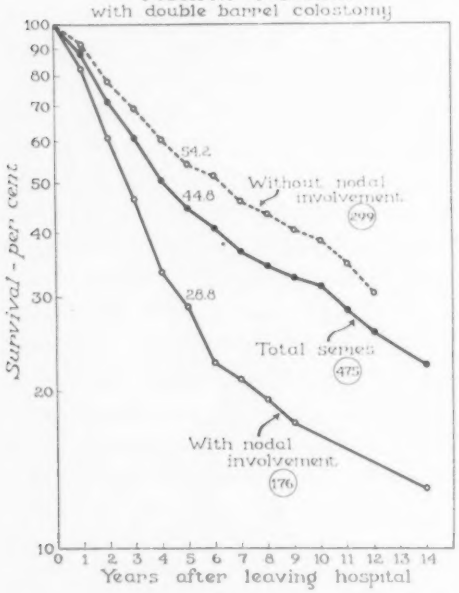


FIG. 9.—Survival rates in 475 cases in which a radical posterior resection was performed. This figure is a complement to figure 7, for these are the cases in which the lesion was too low for performance of the operation of anterior resection. This figure includes the lesions in the distal 6 cm. of rectum plus those occurring up to 10 cm. from the dentate line, in which the lesion was too extensive for anterior resection. The curves show that resection of lesions of the terminal portion of the rectum is attended by a poorer prognosis and that nodal involvement in this region is of graver significance than in cases in which anterior resection could be performed.

The five-year survival rate in the series of cases of posterior resection was 44.8 per cent. This operation is considered inadequate by many authors. Yet, when properly carried out, it is much more radical locally than combined abdominoperineal resection and can be as radical along the pelvic mesocolon. The corresponding five year survival rates for the combined operation were, as stated previously, 40.7 per cent for lesions 0 to 4 cm. and 43.6 per cent for lesions 5 to 9 cm. from the dentate line. Figure 9 also gives the survival rates for posterior resection, divided according to lesions with and without nodal involvement. The five-year survival rate of 28.8 per cent for cases in which there was nodal involvement as compared with 54.2 per cent for those without nodal involvement shows how much poorer the prognosis is in the presence of lesions of type C (Dukes) in the low rectal region. Carcinoma in this region occupies a very strategic position,

straddling the anastomosis between the portal and systemic venous systems. In addition the spread that takes place along the lateral efferent lymphatics accompanying middle and inferior hemorrhoidal vessels, along the sacral and internal iliac nodes and along the base of the broad ligaments in the female, makes attempts to extirpate the lesion discouraging indeed. In practice, resection of the node-bearing tissue between the pelvic fascia and pelvic peritoneum is usually inadequate. The operation of abdominoperineal proctosigmoidectomy is deficient in these respects and also fails to excise sufficient perianal tissue.

SUMMARY

Anterior resection for removal of carcinomas of the upper part of the rectum and lower part of the sigmoid was performed in 426 cases from 1930 through 1947. While there is a slight predominance of males in the series, the female patients tend to be younger and their lesions tend to be of higher grade and closer to the dentate line. There were 25 deaths among the 426 cases, giving a mortality rate of 5.9 per cent. In 270 resections since the present method of preoperative and postoperative management has been used there were 7 deaths (2.6 per cent). Of 272 patients, the five-year survival rate was 67.7 per cent. Comparisons of the mortality and survival rates according to the location of the lesions in various segments of the bowel revealed that the operation is sufficiently safe and radical for lesions of the upper half of the rectum. In cases of adenocarcinoma of the mucous (colloid) and papillary types the prognosis is poorer. The signal improvement in the operative mortality rate in colonic surgery in the past ten years has not been as marked for lesions in the rectum as immediately above that region. Whereas, ten years ago operations for rectal lesions were safest, this no longer is true. The survival rate after resection of low rectal lesions is poorer than that following resection of lesions higher in the bowel. This results from the increase of nodal involvement and greater difficulty in resecting the region of spread. The lesions covered by this study are considered in terms of their distance from the dentate line because of the foregoing consideration and because the possibility of saving the sphincter is determined by this distance.

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THE SIGNIFICANCE OF THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH HYPERTHYROIDISM*

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ONCE THE CLINICAL PICTURE of hyperthyroidism becomes manifest in association with nodular or diffuse hyperplastic goiter (with or without exophthalmos) the diagnosis soon becomes apparent. Nevertheless, when thyroid enlargement is not prominent, when complicating and even confusing factors are present, and when the symptomatology exhibited is minimal, a true clinical evaluation of thyroid function often becomes difficult. This problem is particularly pertinent in those regions where goiter is endemic.

In Central Ohio, which lies within the "goiter belt", nodular goiter is frequent; moreover, these patients, at times, have *non-thyroid hypermetabolic diseases* which cause them to have elevated basal metabolic rates and even to present symptoms suggestive of hyperthyroidism. Essential hypertension and varying degrees of cardiac failure are frequently found in association with nodular goiter. Thyroidectomy, undertaken when such complicating diseases are not clearly differentiated and under optimum control may prove disappointing. Various psychiatric disturbances, and particularly anxiety states, present interesting diagnostic problems when nodular goiter is also present. Symptoms arising in association with the menopausal syndrome are of similar concern. Frequently the basal metabolic rate is elevated in those suffering with carcinoma or similar hyperplastic neoplastic diseases, such as the leukemias.

Much of the confusion encountered in making a diagnosis of so-called "borderline" hyperthyroidism has arisen because there have been developed but few direct objective methods for measuring thyroid function itself. The BMR is a measure of oxygen consumption, the end result of a great many oxidative processes, and not necessarily of that alone associated with the transport, utilization and breakdown of the thyroid hormone. Since the thyroid gland is so intimately related to the metabolism of iodine, numerous studies have been made in an attempt to correlate the amount of iodine in the blood with the BMR in patients with thyroid disease. It was soon learned that the total blood iodine was labile and also varied directly with the iodine intake. Consequently, more recent investigation in this field has dealt largely with the protein-bound fraction of the whole-blood, plasma or serum iodine. Our methods for the acetone separation of the whole-blood iodine into protein-bound and inorganic fractions have been presented.[1, 2, 3, 10]

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THE PROTEIN-BOUND (ACETONE INSOLUBLE) BLOOD IODINE AS AN INDEX OF THYROID FUNCTION

Two necessary qualifications which any blood iodine fraction should possess in order to represent a satisfactory index of thyroid function, are: *first,* that it should increase along with the BMR following the administration of thyroid-stimulating hormone; and, *second,* that it should decrease along with the BMR when elaboration of the thyroid hormone is blocked by means of goitrogenic agents such as propyl thiouracil.

Figure 1 illustrates the response of the BMR and the protein-bound blood iodine * to the administration of thyroid-stimulating hormone in man. The

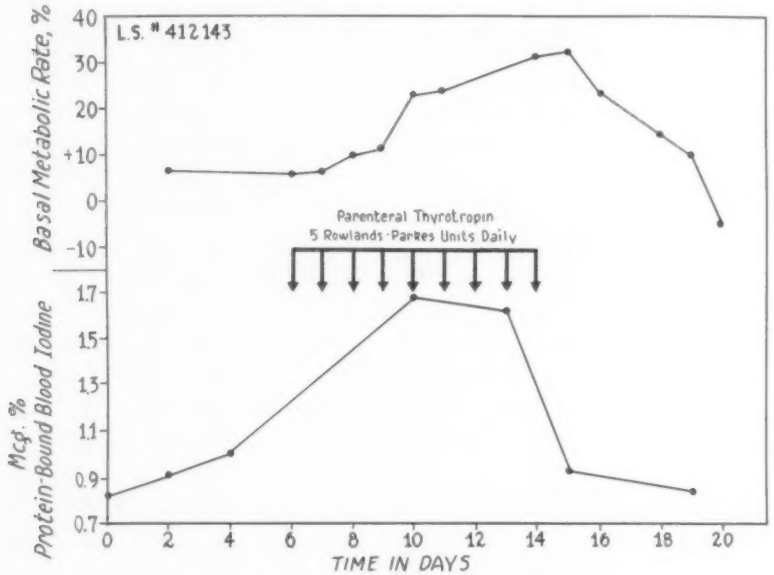

FIG. 1.—Response of the protein-bound blood iodine and of the basal metabolic rate to thyroid stimulating hormone.

peak of the PBI is reached following 5 days of thyroid-stimulating hormone therapy after which it decreases. Characteristically, the BMR rises at a somewhat slower rate, reaching its peak on the 10th day, after which it slowly declines. The decrease of the PBI on the 5th day is illustrative of the refractory response to thyroid-stimulating hormone. Hertz and Roberts [4] found that following thyroid-stimulating hormone administration to the rabbit, the BMR rose to its maximum level on the eighth day of therapy. Our findings in man are similar.

Following Astwood's introduction of thiouracil as a chemotherapeutic agent to block the production of thyroid hormone,[5] many problems in thyroid

* Referred to hereafter as PBI.

physiology were again investigated. By preventing the manufacture of thyroid hormone presumably by blockade of one or more enzyme systems within the thyroid cell, thiouracil administration is followed by an attendant decrease in the PBI and BMR. The literature concerning the experimental data pertaining to the role of thiouracil and its allies in the treatment of hyperthyroidism has recently been critically analyzed.[6] It is the conclusion of qualified observers that the PBI decreases following administration of those goitrogenic agents.

Figure 2 demonstrates the usual response of the PBI to propyl thiouracil in a patient presenting diffuse hyperplastic goiter with hyperthyroidism. Note the initial decline of both BMR and PBI. Each successive cycle during goitrogen therapy is separated from its predecessor by a greater interval of time. The response of the BMR and PBI are essentially the same in toxic nodular goiter.

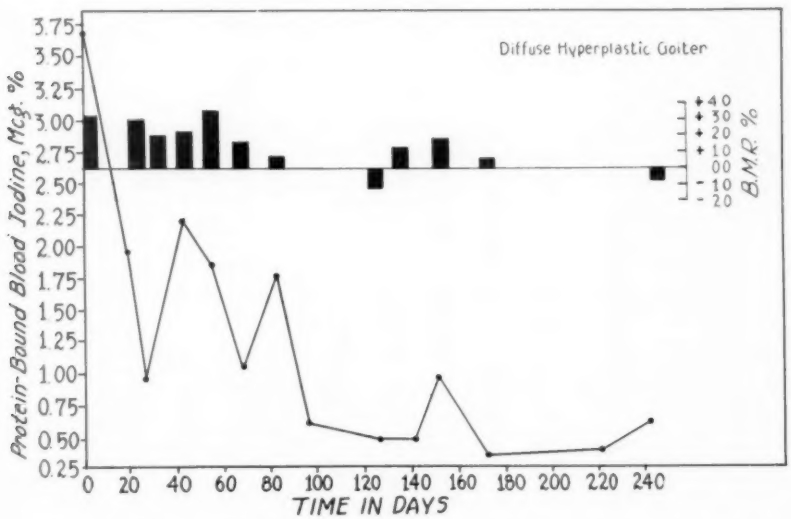

FIG. 2.—Response of the protein-bound fraction of the blood-iodine and of the basal metabolic rate to the administration of 200 mg. cyclopropylthiouracil daily (E.M. at K. H.).

On the basis of studies similar to these we have concluded that the PBI increases characteristically following the administration of thyroid-stimulating hormone and conversely decreases when thyroid hormone formation is blocked by the thiouracil-like drugs. Thus, the PBI may be regarded as a clinical index of thyroid function. Moreover, when the iodoprotein normally occurring in the human thyroid gland, normal human thyroglobulin, is added to normal human serum, and this serum is then fractionated with acetone, the thyroglobulin is quantitatively recovered in the protein-bound fraction.[7]

Previous studies have ascertained that the average normal BMR for the region of Central Ohio is minus 5 plus or minus 8 per cent.[8] Similarly the

average normal total blood iodine concentration equals 4.2 plus or minus 1.2 mcg. per cent.[9] The average normal protein-bound blood iodine (acetone insoluble) is 0.88 plus or minus 0.2 mcg. per cent.[10] This fraction is significantly decreased in patients with hypothyroidism.[10]

We have recently correlated the relations of the PBI and BMR with those symptoms suggestive of hyperthyroidism occurring in 178 consecutive patients with nontoxic nodular goiter.[11, 12, 13] The PBI increases progressively from 0.51 mcg. per cent in those with basal metabolic rates below minus 21 per cent to 1.32 mcg. per cent in those exhibiting basal metabolic rates above plus eleven per cent. Moreover there is a significant *linear* relation between the BMR and the PBI. 66.8 per cent of our patients presented symptoms

TABLE I.—*Toxic Nodular Goiter*

Distribution of patients according to standard deviations of the basal metabolic rate and the protein-bound blood iodine

(Average Normal BMR = minus 5 ± 8%. Average Protein-Bound Blood Iodine* = 0.88 ± 0.2 Mcg. per cent)

BMR %	+3 to +11	+11 to +19	+19 to +27	+27 to +35	+35 to +43	+43 to +59	Above +59	
PBI* Mcg. % ...	1.27	1.65	1.85	1.94	2.16	2.46	3.33	
No. of Patients in each Basal Group..	14	12	16	26	17	19	10	Total Patients 114
% of each Group with PBI above 0.88 Mcg. %	85.7	100	100	100	100	100	100	Total Patients with PBI above 0.88 Mcg. % = 105 or 91.2%
% of each group with symptoms	93	91	100	96.1	100	84.2	90	% of Total Patients with one or more symptoms suggestive of Hyperthyroidism 93.8
% of each group with PBI above 1.08 Mcg. % the upper Normal limit	57.1	100	93.7	92.3	90	100	100	Total Patients with PBI above 1.08 Mcg. % = 102 or 89.4%

* PBI = Protein-Bound Blood Iodine

suggestive of hyperthyroidism and of these 70 per cent had elevations of the PBI while only 47 per cent had elevations of the BMR. Consequently, we concluded that the PBI is a better index of thyroid function than the BMR alone.

Symptoms suggestive of hyperthyroidism, listed according to their positive correlations to an elevated PBI, are a pulse of 90 or more per minute, palpitation, weight loss, weakness, nervousness and emotional instability. Patients with nodular goiter in the region of Central Ohio having either (a) a BMR of plus 3 per cent or above and a PBI of 1.2 mcg. per cent or above, or (b) symptomatology suggestive of hyperthyroidism and a PBI of 1.2 mcg. per cent or above, appear to be potentially hyperthyroid.[11, 12, 13]

Hypertension, organic heart disease, neurocirculatory asthenia, anxiety states as well as other psychoneuroses, neoplastic diseases and certain other endocrine disturbances such as acromegaly and adreno-cortical disturbance, may mimic hyperthyroidism.[14-19] By using the PBI as a diagnostic aid it becomes possible to differentiate the hypermetabolism (elevated BMR, but euthyroid) exhibited by the above conditions from true hyperthyroidism.

In hyperthyroidism, the PBI will as a rule be elevated, but in the hypermetabolic states the PBI will be normal or even below, unless hyperthyroidism is *also* present. Rose [20] has emphasized that hyperthyroidism may be associated with basal metabolic rates consistently within normal limits. The use of the PBI in evaluating the problem which this raises has been discussed,[13] while the presence of hyperthyroidism may be detected by the criteria previously mentioned.

THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH TOXIC NODULAR GOITER

Other investigators agree that the protein-bound blood or serum iodine is elevated in hyperthyroidism.[21, 22, 23] Using 114 patients with untreated,

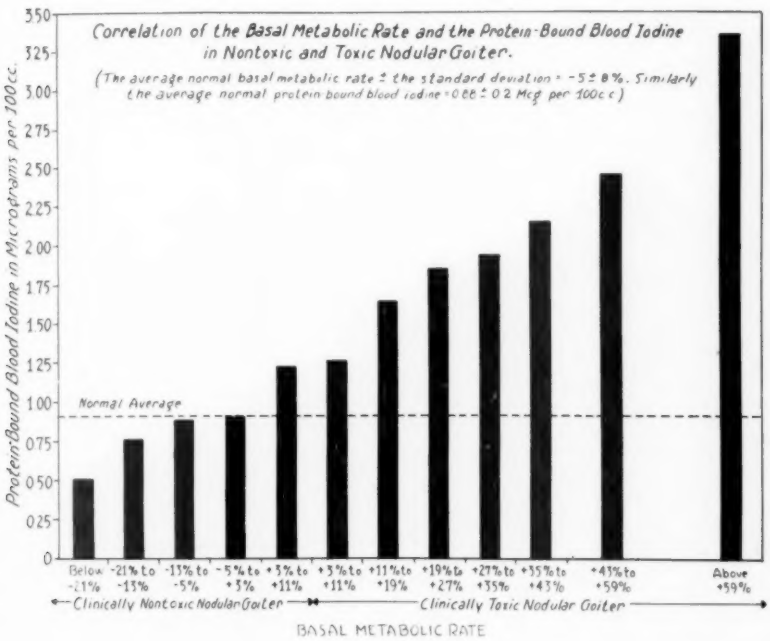

FIG. 3.

uncomplicated, clinically toxic nodular goiter, a detailed correlation of the PBI and BMR has been made and is here presented.

Table I summarizes the distribution of the 114 patients according to standard deviations * from the average normal BMR. The average PBI progressively increases from 1.27 mcg. per cent in those having basal metabolic rates between plus 3 and plus 11 per cent to 3.33 mcg. per cent in those having basal metabolic rates above plus 59 per cent. A comparison of these

* The average normal BMR is minus 5 plus or minus 8 per cent, i.e. the *standard deviation* is 8 per cent.

data with those previously found for nontoxic nodular goiter [11, 12] is presented in Figure 3. The five black bars at the left of the graph illustrate the relation of the BMR to the PBI in nontoxic nodular goiter, while the remaining bars to the right portray a similar relationship for nodular goiter with hyperthyroidism.

A significant, parallel, linear relationship exists between the PBI and the BMR in toxic nodular goiter as well as in the nontoxic type. However, there is considerable overlapping of the clinical diagnosis (either toxic or nontoxic) when the BMR ranges between plus 3 and plus 11 per cent. Consequently, the average PBI of patients having such basal metabolic rates and clinically judged to be nontoxic was compared to a similar group clinically

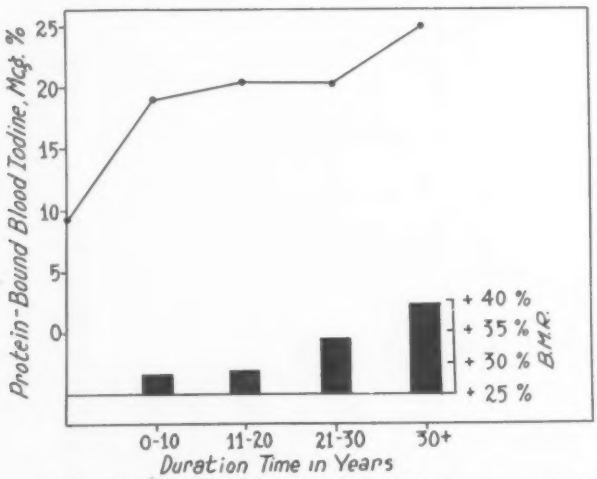

FIG. 4.—Toxic nodular goiter. The basal metabolic rate and the protein-bound blood iodine for each ten year period of goiter duration.

judged to be hyperthyroid. In the former group, the average PBI was 1.21 mcg. per cent, while in the latter it was 1.27 mcg. per cent. The difference was thus less than that of the experimental error. This subtle development of hyperthyroidism in association with the so-called 'harmless goiter' has long been suspected [24] and is here unmasked by determinations of the protein-bound blood iodine. Confusion arising in making a diagnosis upon such patients will be diminished if the significant symptomatology found is correlated with an elevated protein-bound blood iodine.

Further evidence that toxic nodular goiter develops as a sequel to its nontoxic predecessor is found in the correlation between the duration of the goiter, the PBI and the BMR, Fig. 4. The average PBI increases from 1.86 mcg. per cent during the 0-10 year period to 2.50 mcg. per cent in those having had goiter for 30 or more years. In nontoxic nodular goiter patients a similar tendency for the PBI to increase with the duration of goiter is also present.[12, 13]

A significant per cent of the symptomatology suggestive of hyperthyroidism presented by patients with nontoxic nodular goiter has been found to be associated with a BMR of plus 3 per cent or above and with a PBI of 1.2 mcg. per cent or above .[12, 13] Of the 114 untreated, uncomplicated patients with toxic nodular goiter 91.2 per cent had PBI levels above the normal average of 0.88 mcg. per cent, while 89.4 per cent had levels above the upper limit of normal (1.08 mcg. per cent). Symptoms suggestive of hyperthyroidism were exhibited by 93.8 per cent of the entire group.

TABLE II.—*Diffuse Hyperplastic Goiter.*

Distribution according to two S. D. limits of the basal metabolic rate and correlation with the protein-bound blood iodine

BMR %	−5 to +3%	+3 to +19%	+19 to +35%	+35 to +51%	+51 to +67%	+67 to +83%	Above +83%
No. of Patients in each group..	4	13	22	16	14	13	8
Average PBI Mcg. %	1.53	1.96	2.07	2.10	2.98	3.15	3.38
% of each group with one or more symptoms of Hyperthyroidism	100	100	100	100	100	100	100

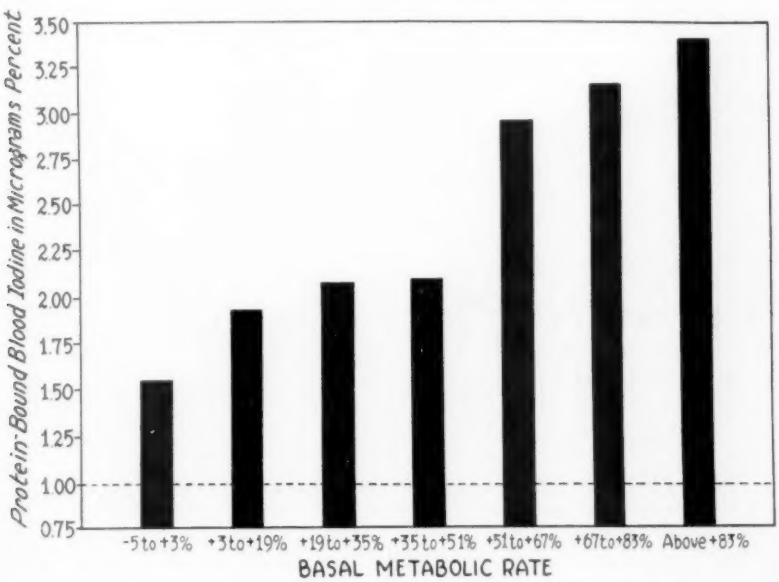

FIG. 5.—Diffuse hyperplastic goiter. Correlation of the basal metabolic rate and the protein-bound blood iodine (The average basal metabolic rate ± the standard deviation = 5 ± 8%. Similarly the average normal protein-bound blood iodine = 0.88 ± 0.2 micrograms per cent.).

THE PROTEIN-BOUND BLOOD IODINE IN PATIENTS WITH DIFFUSE HYPERPLASTIC GOITER WITH HYPERTHYROIDISM

For the purposes of this paper, *primary* hyperthyroidism is defined as hyperthyroidism associated with diffuse hyperplastic goiter with or without

exophthalmos. Ninety consecutive patients with untreated, uncomplicated primary hyperthyroidism have been studied.

Table II summarizes the distribution of the 90 patients according to two standard deviations of the BMR and further lists the average PBI for each basal group. The PBI progressively increases from 1.53 mcg. per cent in the minus 5 to plus 3 per cent basal group to 3.38 mcg. per cent in the group having basal metabolic rates above plus 83 per cent, Fig. 5. It is striking that within the upper normal BMR range (minus 5 to plus 3 per cent) the PBI average is almost twice normal.

In general, (compare Table I with Table II) the average PBI levels for the various basal groups of those with primary hyperthyroidism are higher than for the similar groups having nodular goiter with hyperthyroidism. This presumably indicates a more severe type of hyperthyroidism. As a consequence, the incidence of symptoms is higher. *All* of the patients with diffuse hyperplastic goiter with hyperthyroidism presented one or more

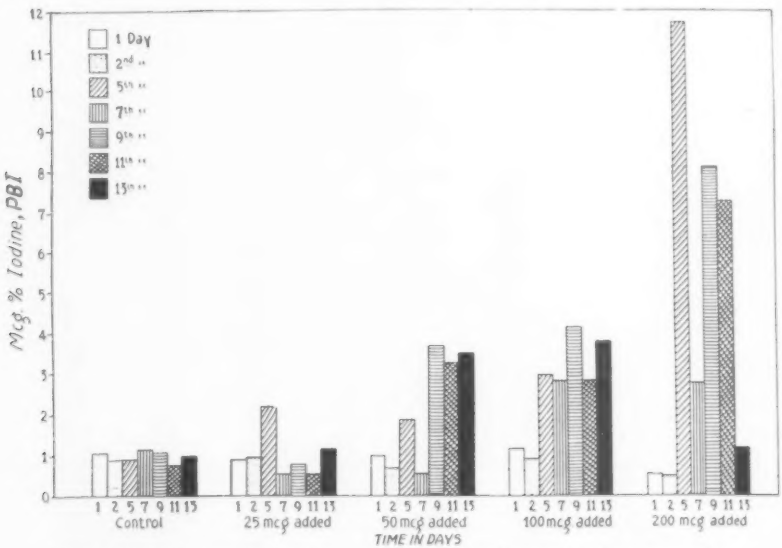

FIG. 6.—Effect of increasing amounts of iodine, added as potassium iodide, upon the protein-bound fraction of the blood idoine.

suggestive symptoms. A linear relationshp between the PBI and the BMR also exists in primary hyperthyroidism, but at a higher level than that found for toxic nodular goiter.

Of those with hyperthyroidism associated with nodular goiter, 93.8 per cent presented symptoms; of those with diffuse hyperplastic goiter with hyperthyroidism, 100 per cent presented symptoms. However, there is a greater incidence of symptoms in the primary type of hyperthyroidism than is apparent by comparing only the number of patients with symptoms. Data pertaining to correlation of the PBI with the symptomatology will be presented elsewhere.

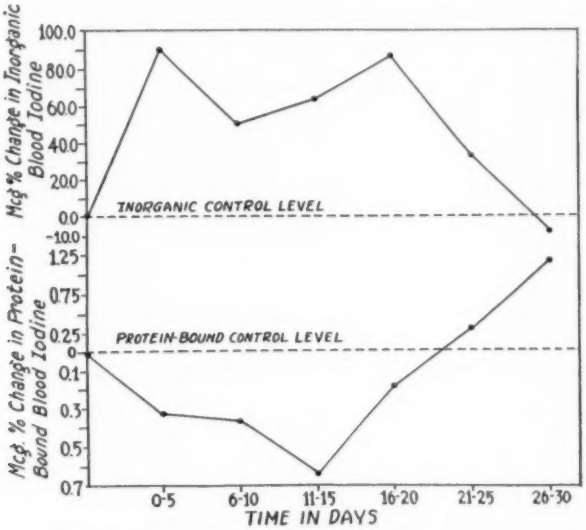

FIG. 7.—Diffuse hyperplastic goiter. Micrograms per cent change in the blood iodine fractions following iodine administration, 100 Mg. daily as potassium iodide.

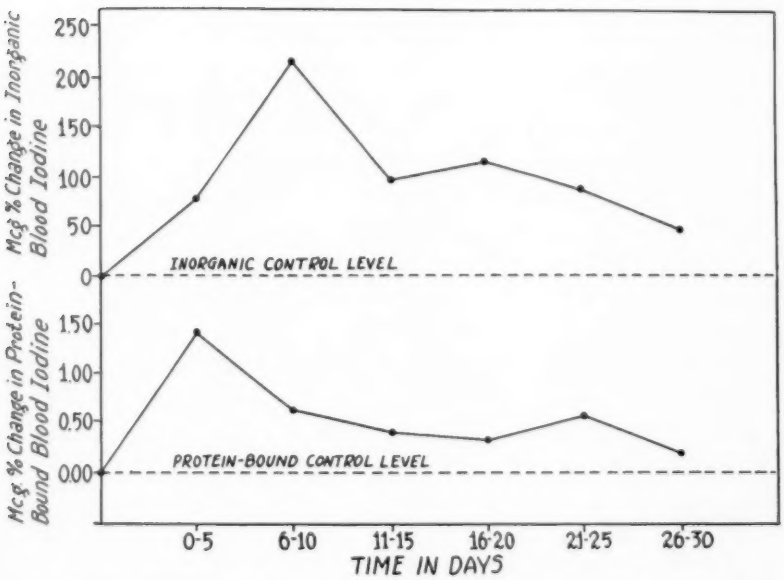

FIG. 8.—Toxic nodular goiter. Micrograms per cent change in the blood iodine fractions following iodine administration. 100 mg. daily as potassium iodide.

RESPONSE OF THE INCREASED PROTEIN-BOUND BLOOD IODINE IN HYPERTHYROIDISM TO CONTINUED IODINE THERAPY

Many investigators have studied the varying phases of the iodoproteins.[25-30] Thyroxine has been isolated from artificially iodinated casein, and optimum results were obtained when four atoms of iodine per molecule of tyrosine were added.[31, 32, 33] Similarly, thyroxine-like and diiodotyrosine-like peptides have been isolated from iodoproteins prepared from serum proteins *in vitro*.[29] The Schardinger enzyme may be intimately concerned with such biologic iodinations.[34]

Following iodine therapy of hyperthyroidism, Salter noted 'spurious' elevation of the protein-bound serum iodine but thought it a chemical artefact; however, he reproduced the phenomenon *in vitro*.[39, 40] In order to determine the relation of such a type of protein iodination to the PBI, we have added varying amounts of potassium iodide to human whole-blood *in vitro*. Fractionation with acetone was then carried out after varying intervals of time.

Figure 6 demonstrates that but little iodination of protein occurs following this procedure, until the total iodine concentration reaches 100 mcg. per cent; further, a striking increase in the protein-bound fraction occurs on the fifth day, strongly suggestive that the reaction at first proceeds according to a 'lag phase' and then by a 'log phase.' This lends support to the premise [34] that certain enzymes play a role in such iodinations.

When the average response of the PBI to continued iodine therapy in primary hyperthyroidism is compared to that of toxic nodular goiter, a striking difference becomes apparent. The average response in primary hyperthyroidism, Fig. 7, is in accordance with the present accepted concepts of the mechanisms of the iodine-induced remission in hyperthyroidism. It is likely that iodine inactivates thyrotropin [35] and temporarily inactivates enzyme systems releasing thyroid hormone from the thyroid follicles.[36, 37] The average response in toxic nodular goiter Fig. 8, mirrors the level of the inorganic blood iodine, and is similar to the response noted following the *in vitro* addition of potassium iodide to blood. *It is difficult to explain these variances unless fundamental differences in tyrosine metabolism, diiodotyrosine and thyroxine turnover and thyroglobulin metabolism exist between the two types of hyperthyroidism.*

Taurog and Chaikoff [38] have reported that following iodine administration to rats, the level of the protein-bound plasma iodine is dependent upon the thyroxine content of the thyroid gland, and is limited by the capacity of the thyroid to produce thyroxine. Our data indicate that the iodination of protein may occur within the blood itself.

SUMMARY AND CONCLUSIONS

1. The protein-bound (acetone-insoluble) blood iodine is presumably thyroglobulin-like in nature.

2. The PBI increases following the administration of thyroid-stimulating hormone to man; conversely, it decreases when thyroid function is blocked by administration of the goitrogenic drugs. It thus becomes a clinical measure of thyroid function.

3. There is a progressive linear relation between the BMR and the PBI in uncomplicated nodular goiter. Determination of this relation unmasks the development of hyperthyroidism in previously quiescent nodular goiters.

4. Hyperthyroidism is probably associated with nodular goiter in Central Ohio once the BMR exceeds plus 3 per cent and the PBI exceeds 1.2 mcg. per cent, or when suggestive symptoms are present and the PBI exceeds 1.2 mcg. per cent.

5. The criteria of conclusions 3 and 4 provide a diagnostic aid for measuring the onset of hyperthyroidism, and for differentiating early hyperthyroidism from other diseases mimicking it.

6. A linear correlation exists between the PBI and BMR in primary hyperthyroidism, but at a higher level than in toxic nodular goiter.

7. Symptoms presented in hyperthyroidism have been correlated with the PBI and the BMR. The incidence of all symptoms in primary hyperthyroidism was 67.1 per cent more frequent than in toxic nodular goiter in the group of patients studied.

8. After iodide therapy, the average response of the PBI in primary hyperthyroidism differs from that of toxic nodular goiter. In the former, the average response follows well established lines, while in the latter the response parallels that noted following the addition of iodide to whole blood *in vitro*. The significance of this finding is uncertain.

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DISCUSSION.—DR. FRANK H. LAHEY, Boston: This is a fine demonstration of the value of blood iodine studies, particularly in doubtful cases. I discussed a paper of Dr. Curtis' similar to this, a short time ago, and in it have said that if one has a research laboratory such as he has and we have, concerned with the study of blood iodine, then these methods are readily available. Blood iodine studies are, however, time-consuming, they are expensive and they are open to a great possibility of error. For that reason I wish to present another method of separating patients with falsely elevated metabolisms and those with truly elevated metabolisms. Dr. Elmer C. Bartels, of the medical department of the Clinic, has developed this method. He has shown that if patients with falsely elevated metabolic rates are placed under pentothal anesthesia, such a metabolism can then be demonstrated to be at a truly normal level. He has also shown by doing metabolisms on patients with known normal basal metabolic rate, that during the determination under pentothal, there is no elevation of the basal rates. This is a valuable method to employ in the doubtful case in which the basal rate is persistently elevated but the patient lacks the clinical evidences of hyperthyroidism to go with it.

DORSAL CORDOTOMY FOR PAINFUL PHANTOM LIMB*

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FOLLOWING THE AMPUTATION of a major portion of an extremity the patient usually experiences the sensation that the missing part is still present. This has been aptly termed phantom limb. In most instances, the ghost part is not particularly bothersome and adaptation to the new body pattern ensues within a few months after the amputation. In some, however, the phantom becomes the source of considerable distress or even intractable pain. Although the ghost is seldom a precise replica of the amputated part, it often bears a strong resemblance to it. Some patients describe the phantom as a small hand or foot attached to the end of the stump of an arm or thigh, without intervening forearm or leg. In others, the false image assumes an unalterable distorted posture and may be the source of continuous cramp-like pain. Various descriptions of the phantom are given by patients and in some it is logical to attribute the complaints to stump neuromas or causalgia.

It does not seem at all surprising that there is a perpetuation of the patient's concept of his own body image after the sudden removal of or somatic denervation of a part. Each individual in the process of growth and maturation comes to appreciate a normal body pattern for himself. If he were born without an extremity there would not be a phantom of the missing part since it was never included in the normal body pattern. In other words, that which he had never had would not be missed. This we have found to be the case. Considering one's ability to adjust psychologically as well as physiologically to altered body patterns, it is readily understandable that a phantom of a part removed persists for a period following its removal. After weeks, months, or in a few years, this phantom gradually recedes from the conscious state but sometimes it can be recalled, as expressed by one patient who sustained a traumatic amputation some 50 years before. "I can always call it (the phantom) back by thinking about it". Moreover, the prominence of the hand or foot in the phantom may be logically explained by the anatomic fact that these parts have a much greater cerebral representation than the forearm and leg. Be that as it may, our critical interest in phantom limb stemmed from our unsuccessful attempts to treat patients with cramp-like pain allegedly due to an unalterable posture of the phantom hand or foot. After running the gamut of sympathetic ganglionectomy, rhizotomy and anterolateral cordotomy in a somewhat empirical manner and without success, it occurred to us that possibly division of a part or all of the dorsal

column of the spinal cord on the side of the phantom might deprive the patient of a knowledge of the position of the ghost part and thereby eliminate the pain.

From our limited experience up to this point it was evident that patients with phamtom limb presented a great variety of complaints. Success had followed the first dorsal cordotomy, but our knowledge of the problem was too meager and the available recorded information so vague that a critical analysis of the subject seemed indicated before proper selection of patients for this operation could be made. It was therefore decided to study a series of patients of variable age who had for one reason or another lost an extremity or extremities either by accident or by elective surgical amputation. Ample material as to numbers was available at the Kings County Hospital; however, the majority of the patients in this institution subjected to major amputation were in the fifth and sixth decades of life and the extremity or extermities had been amputated for some sort of primary vascular disease. We were most fortunate to have placed at our disposal by Dr. George Deaver, patients undergoing rehabilitation at the Institute for Crippled and Disabled, New York City, since here were found an intelligent group coming from many walks of life. The amputations had been performed from a few months to several years prior to interrogation. In addition to the material from the Kings County Hospital and that studied at Doctor Deaver's clinic, a group of individuals born without extremities were questioned and the results included in this series.

Altogether there were 150 subjects, 137 with surgical amputations and 13 born without one or more extremities. Among the 137 patients comprising the surgical group, 159 extremities had been amputated. There were 115 with a major part of a single extremity absent and 22 with multiple amputations. Patients with language difficulties due to foreign birth and those with intellectual alterations interpreted as the result of senile changes were excluded as unfit for study. Included in the series were lawyers, physicians, dentists, artists, school teachers, laboratory technicians, mechanics and laborers. A detailed description of the phantom part was obtained from each and the stump was carefully examined in every case. Eighty-two patients in the surgical group had lost the extremity two or more years prior to the time of the examination. All of these patients were self-supporting and well adjusted to their handicaps. Thirty-three others had been subjected to amputation from six months to two years prior to the present study. Many of the patients in this category were still in a stage of physical rehabilitation, although complete healing of the stump had occurred in all. The remaining 22 patients comprised those with relatively recent amputations. In the majority of these the extremity had been removed only a few weeks prior to this study and in many, complete healing of the amputation site had not occurred. The reason for absence of the extremities is shown in Table I.

CONGENITAL ABSENCE OF AN EXTREMITY OR EXTREMITIES

There were 13 subjects in the series born without the whole or a major part of one or more extermities, a total of 17 missing extremities occurring in this particular group. In 11 of the subjects part of one or both upper extremities was missing, in one an entire lower extremity and in the remaining subject a major portion of both upper extremities as well as a part of a lower extremity were absent. Phantom-limb had never been present among any of these although such a phenomenon was well known to several of them.

PHANTOM OF THE UPPER EXTREMITY

The most striking examples of phantom limb occur after the removal of all or a major part of an upper extremity. Usually the description given by these patients is far more elaborate and vivid than that after a loss involving the lower extremity. The sensory ghost is often present continuously for many years and in some shows practically no tendency to disappear.

TABLE I.—*Reasons for Absence of Extremities*
150 Patients

Congenital absence	13
Occlusive vascular disease	70
Traumatic severance	44
Primary infection	14
Extensive burn	3
Congenital deformity	3
New growth	3

A total of 19 surgical amputations of the upper extremity were studied and phantom limb was present in 17 instances. The amputation had been performed above the elbow in nine and below the elbow in ten. Three of the 19 had sustained accidents that required amputation during infancy. A typical example of the syndrome of phantom limb as it occurs following the loss of an upper extremity is illustrated by the following history.

C. T., a 51-year-old physician, was wounded in the right elbow by a charge of buckshot while on a hunting trip in Mexico. The lower arm and elbow were avulsed leaving the distal part hanging by a few shreds of tissue. There was no loss of consciousness. There was severe pain in the shattered part. Some twelve hours after injury the damaged extremity was amputated four inches below the shoulder. Directly after awakening from the anesthesia there was felt a phantom forearm and hand. The forearm seemed to be flexed and internally rotated while the hand was extended at the wrist. The fingers were held in extension and pursed together at their tips. The ghost hand appeared to be situated near the elbow with the forearm shortened. The hand, especially the fingers, was described as being the outstanding part of the phantom. The fingers could be "moved" without difficulty but usually they remained straightened out and pressed together. The entire hand felt uncomfortable and heavy as though it were immersed in mercury. Our examination was

carried out one year after the amputation. No change in the phantom limb had occurred during this period.

Usually upon recovery from the anesthetic or within a day, regardless of the level of amputation (through the forearm, arm or at the shoulder joint) there was felt a phantom hand and wrist that seemed to be in the region of the end of the stump but not necessarily attached to the stump. Occasionally parts of the missing forearm, elbow or distal arm were included in the phantom. In one instance the entire missing upper extremity was represented in the ghost. In several, the thumb and index finger were prominent parts but the remaining fingers, the palm, back of the hand and the wrist, while present, were not as vividly represented. In seven of the 19 the phantom felt "like a doll's hand or a baby's hand". In only one of these seven had the extremity been amputated during childhood. In 12 the fingers of the phantom were perceived as closed in a tight fist. In three others, the ghost hand was continuously open but the fingers were firmly pressed together and could not be separated. In one the thumb and index finger were flexed toward each other as though a small object was being held between them. Several of these variable features were disclosed in a single subject.

This unusual and often distorted posture of the phantom part has been commented on by several observers, notably Riddoch.[1] It has been stated that the posture that persists in the ghost represents the last remembered position of the limb prior to its removal. Six of this group could recall with accuracy the precise position of the hand and forearm just before being given an anesthetic for amputation and in only one did the posture of the phantom bear any resemblance to that of the extremity just before amputation. This patient was an 18-year-old male who lost his entire hand by the accidental explosion of a blasting cap which he was holding between the thumb and index finger. The phantom hand, as mentioned above, was felt as if the thumb and index finger were almost approximated and he were still holding the blasting cap but the cap could not be felt between them. The fingers of the ghost have remained fixed in that position for almost three years.

Quite in accordance with the statements that we have made regarding body pattern, is that concerning the perpetuation of a deformity in a phantom. That is, after the amputation of an abnormal extremity, a long-standing deformity will be a part of the phantom. Such is not the case if the deformity has been present only a few months before the extremity is removed. For example, a patient accidentally severed the flexor tendon of a ring finger which eventually resulted in a stiff finger. Seven years later the same hand was caught in a mangle, necessitating amputation just distal to the elbow. After this operation all the fingers of the phantom hand could be "moved" except the ring finger which was still stiff.

In no case in this series did the phantom limb that followed the amputation of an upper extremity of an adult disappear or even tend to fade

away. As stated, there were two subjects in whom phantom did not follow amputation. One, a 19-year-old girl, had lost an upper extremity at nine weeks of age. Another patient lost a right upper and right lower extremity in an accident at two and a half years of age. Now at twenty-nine years of age she too cannot recall ever having a phantom of either part. Another lost both upper extremities in a street car accident at three and a half years of age. In this instance both extremities had been amputated just below the shoulders. He is now forty-five years of age and as long as he can remember there has been a phantom on the left side but none on the right. So it may be said that amputation of an upper extremity before three or four years of age may be followed by a phantom part whereas the loss of an upper extremity during adolescence or adult life is almost invariably followed by the presence of a ghost hand that persists either continuously or intermittently throughout the remainder of the patient's life. In some, the ghost part is the site of intractable pain, interpreted by the patient as being due to cramps attending a distorted position of the part. This will receive further consideration later in this paper.

THE LOWER EXTREMITY

In contrast to the situation following the loss of an upper extremity, the phantom limb which appears after the removal of a lower extremity is less striking and is more likely to disappear spontaneously. There were 103 patients studied with loss of a major portion of one lower and 18 others with loss of both lower extremities. In addition one patient with amputation of an upper and lower extremity has been included in this group. These 122 patients had lost 140 extremities. Phantom limb followed the removal of 125 of these. The amputation had been performed through the thigh in 86 instances and below the knee in the remaining 54.

The following history illustrates the syndrome commonly present after a major amputation of a lower extremity.

I. M., a 22-year-old law student, developed gas gangrene of the left lower extremity following an operation on the knee joint. It became necessary to amputate at the level of the mid-thigh. There was no pain before the amputation was performed. He was brought to the operating room with the extremity lying in full extension and encased in a cast. This was the last recollection he had of the limb before the anesthetic was started. Upon regaining consciousness after the operation he perceived the presence of a phantom limb. The ghost consisted chiefly of a foot and the lower leg. It seemed bent so that when he was lying on his abdomen, the foot felt as though it was suspended above him. When he was lying on his back the foot seemed to be protruding through the mattress. The phantom foot was situated closer to the stump than normally. He felt that he could "move" the big toe of the phantom at will but not the other toes. The entire phantom was "asleep" and numb. The amputation stump healed promptly and he was subsequently fitted with a prosthesis. When the patient was examined five years after the amputation, he stated that the ghost foot had undergone no change except that it was not as vivid as it was when it first appeared.

The phantom part described by the patients in this group with major amputations of the lower extremities consisted mainly of a ghost foot. The big toe was especially prominent. In many patients the heel, the ankle and the lower part of the leg were represented and in a few the knee was also present. In three cases the entire missing limb was present in the phantom. As in the case of the upper extremity, the level of amputation in a lower member seemed to have little bearing on the size of the phantom. As a rule, the phantom seemed to be a replica of the original, however, in four the ghost foot was felt as being smaller.

Various sensations were described as arising in the phantom. Itching and tickling in the toes were mentioned by many patients while crawling, prickling or mild cramping were reported by others. Not uncommonly however, the phantom foot was described as feeling "natural."

In contrast to the abnormal position of the phantom of the upper extremity, the posture of the phantom of the lower extremity was not usually distorted. In most cases the foot seemed to be held at a right angle to the leg while the toes were described as being in the usual position of semi-flexion. In some instances the toes were reported as being cramped and pressed tightly together. A few patients stated that the toes were "bent under the foot". In cases where the toes of the ghost seemed tight or cramped, they felt as if they could not be "moved". In five instances the phantom member seemed to be hanging down under the bed as though it were protruding through a hole in the mattress. As previously noted, in the case of the upper extremity, deformities, especially those of long standing, that existed in the lower extremity before amputation, reappeared in the phantom limb. For example, in one patient, after a severe burn, the leg gradually became acutely flexed as a result of a cicatrix. The extremity was subsequently amputated at the level of the mid-thigh and the phantom which developed after amputation, was that of a flexed leg much the same as the posture assumed by the extremity before operation. There were numerous patients in the series who had lost one or several toes prior to undergoing amputation at a higher level. Only rarely were these losses perpetuated in the phantom.

In most cases the phantom lasted for one or two years. However, there were several exceptions to this. Thus, there were five subjects who still had a well marked phantom after 20 years, while another patient had experienced a phantom for 36 years and still another for 38 years. Usually the sensations associated with the phantom such as itching, tickling and so on, persisted for only a few months and disappeared long before the phantom.

MULTIPLE AMPUTATIONS

Amputations of the upper or the lower extremities bilaterally are usually followed by bilateral phantom parts, although the ghost hands or feet may not be identical. This is true, not only when the bilateral loss occurred as a

result of surgical procedures carried out at different times but also when the amputations were performed at the same time.

There were 22 patients in the series with major amputations of two extremities. In 18, major portions of both lower extremities had been removed, while in three others major parts of both upper extremities had been amputated. In the remaining patient a single upper and lower extremity on the same side had been removed. In one patient both lower extremities had been accidentally severed at the same level just distal to the knee. Although the level of surgical amputation was nearly identical on both sides, the phantom foot was much more in evidence on the left. Furthermore, the toes of the phantom on the left were said to be itchy while those on the right were not. Often the ghost image was more enduring on one side than the other. Also a greater portion of the missing limb was usually represented on one side.

AMPUTATION DURING CHILDHOOD AND ADOLESCENCE

Children. Children may have a phantom limb after the amputation of an extremity. There were 16 patients in the group who were 12 years old or less at the time of amputation. A total of 18 major amputations had occurred in this group and a phantom limb followed amputation in eight cases. The majority of these individuals were adults at the time of this study. As previously stated, the youngest subject with a phantom had lost the upper extremity at three and a half years of age. The youngest patient with a phantom limb following the removal of a lower extremity was four years old at the time of amputation. The phantoms that followed amputations during childhood and that persist into adult life are described as the same regardless of the age at the time of amputation.

Adolescents. There were 12 subjects in this group who had sustained a major amputation while between the ages of 13 and 16 years. A total of 15 major losses had occurred in the adolescent group. All of these patients developed typical phantom limbs. A single upper extremity had been removed in four patients while a single lower extremity had been removed in five others. Two of the remaining patients had sustained a loss of both upper extremities and one other individual had sustained the loss of both lower extremities.

MISCELLANEOUS FACTORS RELATED TO THE AMPUTATION AND THEIR BEARING ON PHANTOM LIMB

It is recognized that the extremities on the dominant side of the body receive preferential use all through life. One might expect then that the removal of an extremity, especially a hand, from the dominant side would result in a more lasting and perhaps a more striking phantom part. This has not been found to be true. The best opportunity to evaluate a phantom part in its relation to limb dominance occurred in those patients who had sustained simultaneous bilateral amputations of upper extremities. There were 11 such individuals in the group. Some of these patients stated that both

phantoms were equally striking, while others could not be sure which was the more prominent. In some instances the phantom on the dominant side was not as well perceived as that on the opposite side. Comparing the lengths of time each ghost endured it was found that the hallucination on the dominant side did not last significantly longer than the one on the other side. Furthermore an analysis of patients with amputations of single extremities showed that limb dominance had very little effect either on the character or the duration of the phantom.

Some observers have stated that amputation through the forearm or leg is more likely to give rise to a lasting phantom limb than an amputation performed more proximal. A comparison of the duration of the phantoms resulting from 64 low-level removals (below the elbow or knee) and 95 high-level removals did not support this statement.

It was found that if an extremity was accidentally severed the resulting phantom was more likely to be enduring. As already noted, the phantom which followed the removal of an upper extremity is likely to last for a longer period than the one which appears after the loss of a lower extremity. Most of the amputations of the upper extremity in this series occurred as a result of accident.

Wound healing, either primary or secondary, seems to have little effect on the occurrence, type or duration of phantom limb. There were 32 amputations in the series where delayed healing of the amputation stump had occurred and 127 other stumps in which primary healing of the operative site had taken place. Furthermore, it was found that poorly constructed stumps did not produce any significant alterations in the phantom limb. Protruding ends of bone, unnecessarily large flaps of tissue or tight flaps were present in some and were often the cause of local pain in the stump. While these features frequently prevented the patient from wearing a prosthesis they apparently had no influence on the phantom part.

PAINFUL PHANTOM LIMB

In the entire series of 159 surgical amputations in 137 patients there were 48 painful phantoms in 47 of these, 38 male and 9 female. A critical review discloses that the level of amputation, the nature of the wound healing, whether the extremity was amputated for a disease process or as a result of trauma, whether the extremity was the dominant one or not or whether the stump tissues were redundant or taut seeemed to have little if any bearing on the two types of discomfort that are subsequently described as transitory and enduring painful phantom. Pain in the extremity prior to amputation seemingly influences the presence of pain in the phantom limb. This was true for both transitory and enduring pain. Of the 38 cases with transitory pain, 26 had severe pain before the extremity was removed. Of the ten examples with enduring pain in the phantom six had severe pain before amputation.

Considering every case where an amputation was followed by a phantom limb, the incidence of painful phantom limb was approximately 30 per cent. The syndrome of painful phantom limb is frequently confused with painful neuroma or causalgia of the stump. Pain arising from neuromas is distinctly local in character. The discomfort in such cases is intermittent and occurs when the end of the stump is mechanically stimulated. The distress is sharp and often electric-like. The pain arising from stimulation of neuromas is frequently referred out to the phantom limb, if present, but does not originate in the ghost part itself. Jumping stump may be associated with the attacks of pain. The discomfort may be promptly abolished by injections of procaine into the painful neuroma. Causalgia of a stump is more apt to occur after amputation of a digit than after the removal of a major portion of an extremity. In a few cases the stump was the site of severe burning pain. In stump causalgia, a light touch often initiates burning pain that may involve the whole stump. These patients will not permit the part to be handled and at times they are unable to bear even the weight of clothing on the stump. Exposure to a cold draught is often sufficient stimulus to initiate pain. On examination the stump in such cases is found to be cold, sweaty, cyanotic and somewhat atrophic.

In reviewing the complaints of the patients in this group with pain in the phantom limb, exclusive of the causalgias and neuromas, it became evident that they fell into two divisions. In the first division the discomfort was transitory and showed a progressive tendency to diminish in severity as time went on. In the second, the pain was enduring and showed no tendency to relent as time passed. In those with transitory pain in the phantom the discomfort was characterized by the presence of bothersome dysesthesias such as numbness, tingling or burning, whereas in those with enduring pain the distress was characterized by an unalterable postural distortion of the phantom member.

TRANSITORY PAIN IN THE PHANTOM LIMB

In 38 instances bothersome distress of a transitory nature was present in the phantom part. In two cases transitory pain in the phantom was associated with loss of an upper extremity while in 36 others the lower extremity was involved.

As stated the discomfort in those considered to have transitory pain was usually described as a sensation of bothersome burning, tingling, coldness, numbness, fullness or occasionally electric shocks in the ghost member. In most instances the pain appeared on the day after operation or shortly thereafter. However, in one instance the pain came 13 years after amputation, in another three years and in another four months after operation. Commonly the discomfort was fairly severe for several weeks after operation followed by a gradual subsidence. In 27 cases the pain had disappeared after 12 months. In seven others, it had totally subsided after 24 months. In the remaining four the distress had persisted for three, five, seven and

ten years respectively, but in each of these the pain was considered to be gradually disappearing. In 12 of the 38 cases the pain in the phantom bore a distinct resemblance to the discomfort present in the extremity before amputation. Among this group of patients with transitory pain in the phantom limb, there were four with bilateral losses of the lower extremities. One patient experienced distress of a temporary character in both phantoms. Two had bilateral phantom limbs but in each instance pain was present in only one side. The remaining patient had a phantom limb on only one side associated with mild pain in this ghost part.

ENDURING PAIN IN THE PHANTOM LIMB

In ten instances, the phantom limb was the seat of enduring and unrelenting pain. In four cases the pain in the ghost member had followed the removal of an upper extremity, while in the other six it developed after the loss of a lower extremity. The following case history is illustrative of this syndrome in the upper extremity.

J. B., a 53-year-old white male, sustained an avulsion injury of the right upper extremity in an auto accident. A few hours later amputation was carried out through the upper arm. He could not recall having any pain in the member prior to its removal. Immediately after awakening from the anesthetic there was a phantom limb. The ghost part was lying in front of his chest and seemed to be situated close to the amputation stump. The lower arm, elbow and forearm were not represented. The fingers of the phantom were held in extension with the tips pressed together. A sensation of cramping was present in the ghost and the fingers felt uncomfortable. Gradually the phantom hand became more distressful so that by the third month after operation the pain was continuous. A pressing and squeezing sensation was now present involving the palm and all the fingers. The fingers were so tightly pressed together that it seemed as though they were being crushed in a vise. The wrist was also painful and felt as though a wire noose had been tightened about it. He discovered that the pain became worse when the weather was inclement. If the end of the stump was accidentally struck, a shock-like sensation radiated out to the ghost part, however, under these conditions the squeezing pain remained unaltered.

The syndrome of intractable pain as related to amputation of the lower extremity is illustrated by this case:

I. S., a 60-year-old white male with obvious arteriosclerosis, developed gangrene of the right foot. The gangrenous toes had become gradually insensitive and they were finally removed without the use of an anesthetic. Shortly afterward a cellulitis of the foot developed associated with severe pain in the entire involved limb. Seven weeks after this the extremity was amputated through the mid-thigh. After recovering consciousness there was a phantom limb. The lower leg and the foot were represented in the phantom. At first the phantom limb was not painful; however, two weeks after operation there was a severe cramping sensation in the ghost foot. Over a period of several weeks this distress gradually became more severe and the phantom felt as though it were being forcibly bent on itself. After great effort the foot could be "straightened" slightly and the pain would temporarily lessen. Narcotics were resorted to and had been continued up to the time of examination.

In every instance where the phantom was the seat of intractable pain the outstanding clinical feature was painful postural distortion of the ghost. As a result of this the patient complained of unrelenting cramping, squeezing or twisting of the phantom part. In a few instances temporary respite from pain followed "voluntary movement" of the ghost. In no case did the distress show any tendency to abate with the passing of time. After the removal of an upper extremity one patient stated that the nails and fingers felt as though they were being dug into the palm of the ghost hand. Another patient stated that his phantom hand was perpetually clenched in a tight fist so that he could not open it. Following amputation of a lower extremity another complained of having the feeling that the toes were being bent into the sole of the phantom foot. Another described his ghost foot as having a tight wire twisted around it and the toes felt as though they were being squeezed. Still another individual stated that his ghost foot felt as though it were encased in a block of cement and that the foot could not be moved.

In each of the ten cases, the distortion of posture involved the distal portions of the phantom. Patients with pain due to such unalterable abnormal posture of the phantom are the ones that may be relieved by dorsal cordotomy.

DISCUSSION

Following the loss of a part of the body, either by operation or accidental trauma in the adult human, there is a perpetuation of the patient's body image. It rarely occurs if the part, especially an extremity, has been removed during early childhood and in our experience has not been present in those in whom the part was removed before the third year of life. It is never present in subjects born without extremities. We find nothing so remarkable about this. In truth, the adult subject who refuses to admit the presence of a phantom limb after the amputation of a major part of it, is to be considered psychologically abnormal. Long-standing deformities of, as well as absence of, digits of a hand or foot that have been established in any particular individual's body pattern should be expected to be perpetuated in the phantom if the extremity of which the abnormality was a part were removed later in life. This too we have found to be the case. This perpetuation of the body pattern that has been called ghost or phantom part, is not what has attracted our attention but the fact that in many instances the phantom is not a replica of the part removed. Especially has our attention been attracted to those patients with pain that is described as residing in a miniature ghost of the part removed and at times resulting from an unalterable cramped posture of the fingers or toes of the phantom hand or foot.

Several theoretical explanations have been proposed for this most remarkable phenomenon, notably that impulses arising from the stumps of the severed nerves upon reaching the cerebral cortex are interpreted as coming from an extremity that is smaller and often distorted. Such a concept seems

untenable. There were ten patients in the present series with phantom limb who were subjected to reamputation of the stump. Sectioning the nerves of the stump at a higher level produced no changes in the phantom. It seems most unlikely that the surgeon could have sectioned the nerve trunks at the second operation precisely as they were divided at the first operation. Moreover, experience has shown that sectioning all the spinal nerves introdurally that supply the stump of an extremity has no bearing on the size or posture of a phantom, nor does such a procedure relieve or change the character of pain that seems to reside in the phantom. One patient in the series sustained a traumatic amputation of the forearm associated with an avulsion of brachial plexus of the same side. The remaining stump of the arm was totally devoid of all sensation yet there was a phantom hand that was described as being in a continuous painfully cramped posture.

Anterolateral cordotomy with resultant loss of pain and temperature of the stump has produced transitory alterations of the phantom in a few, whereas in others there was no change in the size and posture of the phantom nor the character of the pain. This operation has relieved the pain associated with overgrowth of nerve stumps, the so-called painful stump neuromas. It has had very little if any beneficial effect on the burning pain of causalgia. Leriche[2] and Livingston[3] have emphasized the role of the sympathetic nervous system in connection with painful phantom limb. Sympathetic denervation of a stump may favorably influence a painful phantom part for several weeks; however, from our experience, lasting benefit should not be expected to follow sympathetic ganglionectomy.

In 1911, Head[4] reported the disappearance of a phantom limb following thrombotic infraction of the sensory cortex contralateral to the ghost part. Guiterrez-Mahoney[5] has shown that selective excision of a part of the parietal cortex may modify phantom limb and produce transitory reduction in the pain residing in the ghost. We have indicated in a previous report that the cramp-like pain in a phantom hand or foot that has been described by the patient as the result of an unalterable posture in the ghost may be favorably altered by surgical section of the fibers of the dorsal spinal cord on the side of the disturbance. Both of these procedures (parietal cortical ablation and dorsal cordotomy) are designed to deprive the patient of a knowledge of the stump as well as the phantom. Certainly one would not expect that either the cerebral cortical ablation or section of the fibers in the spinal cord that allegedly carry proprioceptive sensibilities would favorably influence pain produced by a neuroma or the other clinical syndromes characterized by pain that may arise from scarring in the end of the stump. It must therefore be clearly recognized that the selection of the patients to be subjected to either of these operative procedures must be made with great care. Approximately 100 per cent of adult patients who lose an extremity will have a phantom limb lasting for variable periods after operation. About one-third of these will suffer from pain in the stump

and/or the phantom and in 75 per cent of these the pain will slowly disappear. A small percentage (approximately 7 per cent of the total number) will have a more or less continuous cramp-like pain in the phantom hand or foot due to abnormal posture of the ghost. It has been our experience to date that complaints of this character coming within a week or so following operation are likely to continue throughout the remainder of the patient's life unless modified by a surgical procedure designed to deprive the patient of a knowledge of the position of the ghost part.

TREATMENT AND RESULTS

Our surgical experience has been limited to dorsal cordotomy. As stated, selection of the patient for operation is of utmost importance. Only those with pain in the phantom due to cramped abnormal posture of the ghost should be subjected to this operation. Six patients have been operated upon, two with painful phantom hands and four with distorted painful phantoms of the legs and feet. The cordotomy for the abnormalities of the upper extremity should be performed at the level of the second cervical spinal segment. The lateral two-thirds of the dorsal column of the cord may be sectioned without disturbing gait or station. For the lower extremity the tractotomy should be performed at the mid-thoracic level and all of the fibers of the dorsal column on the side of the phantom are to be sectioned. With the spinal cord exposed and the arachnoid removed, the dorsal sulci may be identified by dropping some blood on the cord and observing the red blood cells collect in these grooves. An alternate method is to make the sulci prominent by applying a small amount of neutral methylene blue to the surface of the cord. Following dorsal cordotomy there is no demonstrable disturbance in rectal or vesicular sphincters nor motor power of the stump. Appreciation of touch was not altered. In three patients there was impaired but not marked loss of appreciation of vibration of the tuning fork below the level of the section of the spinal cord. Appreciation of passive motion of the stump was impaired in three, however, this mild disturbance disappeared within about three months following operation. Complete loss of the phantom foot and the cramp-like pain resulted in three. In the remaining patient with phantom foot the pain was relieved but "at times the phantom is still there". Hypnotics were no longer used and there was a gain in weight. The results in the two patients with phantom upper extremities were not so good. At least the results are difficult to evaluate. One of these (a World War II veteran) before operation complained of cramp-like pain in a small phantom hand that seemed to be "close to but not connected with" a short stump of the left arm. In addition there was a burning sensation in the phantom that was said to be in the region of the hypothenar eminence. After operation performed by Dr. Frank Turney, the phantom hand was still present and there was "some burning" in the hypothenar region of the ghost. He flatly denied ever complaining of a cramp-like pain

in the phantom, the outstanding distress before operation as recorded by three competent observers. The other patient with painful distorted phantom of the left upper extremity was a none-too-intelligent negro approximately sixty years of age. Before operation there was a complaint of continuous cramp in the ghost hand. He was frequently seen to be holding the stump of the left arm with the right hand. After operation the phantom part was not mentioned by him unless inquired into by the house staff. If asked directly regarding the ghost part it seemed that there was intermittent burning type of pain in the stump of the arm and that the phantom was present if attention was focused on it.

From the results obtained from dorsal cordotomy up to the present time we believe the procedure has merit and its use should be continued. Certainly the results in the patients with phantom foot are most encouraging.

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Discussion.—Dr. Gilbert Horrax, Boston: I think one of the curious things in phantom limb pain is this cramp-like pain in the extremity. Most patients complain that the hand is in an extremely cramp-like position and they cannot get it down. The causalgia-like pain that some of them have, if it is helped by anything, is helped by sympathectomy. Dr. James E. White brought that out, I think, in a discussion of war cases. This cramp-like pain is not helped by sympathectomy, at least in our experience. Cordotomy, in our experience, is useless with these amputation pains. Other procedures have been used, and Dr. Mahoney some years ago did several cortical incisions of the sensory area for the painful phantom. I understand that he has said recently that the pain in those patients returned. I carried out cortical incision in one patient who had bilateral amputation of the upper extremities, doing it on both sides. He was relieved only for a week or two, then the pain recurred and was as bad as ever. I think I was ill-advised to do this so far as that particular patient was concerned, because although we got him off morphine he had become an addict and went back to it eventually. It is my feeling that in a case of that type, probably a lobotomy might succeed, although that remains to be seen. But cortical excisions for this type of pain have not been successful in my hands. Therefore I think that if dorsal cordotomy, which is a relatively simple operation, will eliminate this severe cramp-like pain, Dr. Browder has made a distinct contribution to neurologic surgery.

A COMPARATIVE STUDY OF SUBTOTAL GASTRECTOMY WITH AND WITHOUT VAGOTOMY*†

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THERE SEEMS TO BE LITTLE DOUBT that severance of the vagus nerves to the stomach produces physiologic changes which promote peptic ulcer healing and possibly prevent recurrences in the majority of cases. However, some surgeons have abandoned vagal section as the sole procedure in the surgical therapy of chronic non-obstructive duodenal ulcer because there have been recurrences despite complete vagotomy as verified by negative insulin tests, and because the high incidence of persistent gastric atony frequently required further surgery for correction. The addition of a gastro-enterostomy to bilateral infradiaphragmatic vagotomy usually eliminates the symptoms of gastric motor disturbances. It has long been recognized that gastro-enterostomy per se will heal a duodenal ulcer, but the fact that this operation is followed by a high incidence of jejunal ulceration has minimized its usefulness. Whether the addition of vagus section will prevent this untoward complication will be decided only by future follow-up observations. We, as well as others, are employing this combined procedure in a series of selected cases, and while the results to date appear promising, insufficient time has elapsed to warrant definite conclusions.

Although subtotal gastrectomy of the Billroth II type is still the procedure of choice for duodenal ulcer in many clinics, it has not met with universal approbation. Its critics have stated that in the hands of the average surgeon the mortality is too high and that the end results do not justify the magnitude of the procedure. However, the mortality and morbidity in experienced hands has been markedly reduced in recent years. It is true that following gastric resection some patients fail to gain weight, some are rendered uncomfortable by the dumping syndrome, and a certain number develop jejunal ulceration. The incidence of this latter complication has been reported as between 3 and 9 per cent. Most of these occur in the presence of high free acid values in the gastric contents. If subtotal gastrectomy, which removes the hormonal phase of gastric secretory activity, is combined with bilateral infradiaphragmatic vagotomy, which eliminates the psychic phase of gastric secretion, it is reasonable to predict a further lowering of the acidity or the production of an achlorhydria. Under these conditions, the incidence of jejunal ulcer should be reduced, for it is well known that jejunal ulceration does not occur in the absence of free hydrochloric acid.

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The combination of subtotal gastrectomy and infradiaphragmatic vagotomy for duodenal ulcer is not a new concept. In 1929, Klein[1] published the results of left anterior vagotomy and gastric resection in eight cases of duodenal ulcer with unusually high preoperative acid figures. All cases revealed an achlorhydria to the gruel Rehfuss test within six months after operation. In a control series treated by gastrectomy alone, only 25 per cent developed an achlorhydria. Subsequently in 1934, Winkelstein and Berg[2] reported further studies in 34 cases of duodenal ulcer with high preoperative acidity in which twenty-six, or 77 per cent, developed achlorhydria to gruel following partial gastrectomy and left subphrenic vagotomy.

It was therefore considered logical to combine subtotal gastrectomy with infradiaphragmatic bilateral vagotomy provided the operative risk and postoperative morbidity were not appreciably increased. At first, this combined procedure seemed especially indicated in the duodenal ulcer cases in which bleeding without pain was the predominant symptom, and those in which the preoperative acid studies were unusually high, two categories in which subsequent jejunal erosion and ulcer are most apt to occur. Accordingly, early in 1946, subtotal gastrectomy and complementary bilateral infradiaphragmatic vagotomy were performed on several of these patients without mortality or significant additional postoperative morbidity. Encouraged by the immediate results, the indications were broadened and the combined procedure was performed with increasing frequency. Other similar cases in which subtotal gastrectomy alone was done for duodenal ulcer were used for comparison. It might prove informative to review these two series to determine the advantages and disadvantages of the combined procedure.

This presentation must be considered as a preliminary report for the ultimate results of any ulcer therapy must be based on follow-up studies extending over a period of many years.

The cases studied represent all the duodenal ulcers admitted during the years 1946 and 1947 to the C Ward Service of the Mount Sinai Hospital and to the private service of the senior author, in which subtotal gastrectomy with and without vagotomy were done. All of these cases had had previous medical treatment. The average duration of symptoms was more than 12 years, and the average age of the patients was 45 years. There were 100 such cases, 12 of which had been operated upon previously for acute perforations. Fifty-four patients were treated by subtotal gastrectomy and 46 by subtotal gastrectomy combined with bilateral infradiaphragmatic vagotomy.

The incidence of untoward reactions at the time of operation was minimal in both groups. One case in the gastrectomy series suffered a sudden sharp drop in blood pressure and a rise in pulse rate toward the end of the procedure. A similar change was noted in one patient when the vagus nerves were mobilized and resected. In view of the fact, however, that in this clinic the infradiaphragmatic vagotomy is performed after the gastric resection, these circulatory effects cannot be ascribed to the vagotomy. No other sequelae

such as bradycardia, vagovagal reflex or cardiac arrest were noted. However, in one case, while attempting to mobilize the esophagus, it was partially torn longitudinally. The laceration was sutured, but the vagus nerves were not sectioned. The patient made an uneventful recovery.

There were no deaths in either group in this series.

A comparison of the early postoperative complications revealed some differences between the two series. The postoperative course was rated as minimal, moderate or severe. In the gastrectomy group of 54 patients, 48 were classified as minimal, five as moderate, and one as severe. In the gastrectomy-vagotomy group of 46 cases, 31 were classified as minimal, 13 as moderate, and two as severe.

A summary of the complications in the two series are listed in Table I.

There were six cases with pulmonary complications in the gastrectomy group, all of which were mild; there were ten in the gastrectomy-vagotomy group, eight mild and two severe.

Five cases in the gastrectomy group developed postoperative retention and vomiting, which in two were rather distressing and prolonged. Six patients of the gastrectomy-vagotomy group suffered from similar symptoms but these were severe in only one.

TABLE I

	Subtotal Gastrectomy	Subtotal Gastrectomy and Infradiaphragmatic Vagotomy
Pulmonary	6	10
Vomiting and retention	5	6
Diarrhea	4	5
Distention	1	3
Dysphagia	0	4
Duodenal fistula	1	4
Pelvic exudate	0	2
Subhepatic exudate	0	2
Evisceration with intestinal obstruction	0	1

A mild diarrhea occurred in four patients of the gastrectomy series. However, one of these was obviously due to the effects of jejunal alimentation and subsided promptly when these feedings were discontinued. The gastrectomy-vagotomy series contained five cases with diarrhea. In the only one which was severe, stool cultures revealed that the patient was suffering from a Salmonella infection. Another patient had a penicillin reaction, which produced a rash, fever, and diarrhea. It was felt that for purposes of comparison, these two cases might be discarded. A corrected incidence of diarrhea disclosed three mild cases in the gastrectomy series, and three mild cases in the gastrectomy-vagotomy series.

Marked abdominal distention was noted in only one case of the gastrectomy group, and that occurred in the patient previously mentioned, who had had a complementary jejunostomy. In the gastrectomy-vagotomy series there were three cases with moderate postoperative distention due to peritonitis rather than vagotomy. All of these were observed in patients in whom the duodenal closure had been difficult, and the area had been drained. A temporary duo-

denal fistula developed, and in two of these cases, subhepatic and pelvic exudates resulted, which subsided spontaneously.

Four patients in the gastrectomy-vagotomy group complained of substernal pressure and pain on swallowing which occurred in general about the second postoperative week and lasted for about ten days. It was assumed that this was caused by the reaction to mobilization of the mediastinal esophagus.

Gastric secretion studies before and after subtotal gastrectomy for duodenal ulcer have been previously reported by Winkelstein[3, 4] of this clinic. (Table II.) Postoperative secretion studies in the present gastrectomy series were not routinely performed.

Preoperative gastric secretion studies in the gastrectomy-vagotomy group revealed the usual hyperchlorhydria found in duodenal ulcer patients. The postoperative secretion studies in 39 of the 45 patients in the gastrectomy-vagotomy group are summarized in Table III.

TABLE II.—*Postoperative Secretion Studies After Subtotal Gastrectomy (Winkelstein)*

Test	No. of Cases	Anacid	Free acid Present	Percent Achlorhydria
Gruel	85	47	38	55
Night	21	14	7	67
Histamine	31	13	18	42

TABLE III.—*Postoperative Secretion Studies (Gastrectomy-Vagotomy Group)*

Test	No. of Cases	Anacid	Free Acid Present	Percent Achlorhydria
Gruel	12	12	0	100
Night	20	19	1	95
Histamine	28	21	7	75
Insulin	24	20 (or negative)	4 (positive)	83

TABLE IV.—*Symptomatology 4 to 28 months postoperatively*

	Subtotal Gastrectomy (46 cases)	Gastrectomy-Vagotomy (40 cases)
Pain	3	2
Bleeding	1	0
Vomiting	5	2
Diarrhea	1	5
Dumping	0	1

A comparison of the results of the secretion studies following subtotal gastrectomy reported by Winkelstein with those of the present gastrectomy-vagotomy group reveals a decided increase in the percentage of postoperative achlorhydria.

Despite the small number of patients tested by the gruel Rehfuss, the difference between the percentage of achlorhydrias (Table II and III) is large enough to be considered significant. The gruel test stimulates both the psychic and chemical phases of gastric secretion. After subtotal gastrectomy alone, 55 per cent of the cases were anacid to gruel. The addition of vagotomy produced an achlorhydria in all 12 patients examined. The number of patients

tested by the gruel Rehfuss was small, inasmuch as this test was not done upon patients anacid to histamine.

The night secretion studies in the gastrectomy-vagotomy group revealed achlorhydria in 19 of the 20 patients tested, as compared to 14 of 21 following subtotal gastrectomy. It is significant that the one patient in whom free acid was present in the night secretion gave a hospital insulin test indicating incomplete vagotomy. Postoperative night secretion studies in both these groups reveal an essential difference from those in which vagotomy was employed as a sole procedure. In the latter, the night secretion was definitely diminished both as to volume and acid concentration, but achlorhydria was rarely obtained.

It is difficult to explain the increased incidence of histamine achlorhydria following the combined procedure when compared to gastrectomy alone, since histamine stimulates directly the acid secreting cells. This problem awaits further investigation. The interpretation of the insulin response will be the subject of a future communication.

Although these acid secretion studies are based on a small number of cases, they indicate that the addition of bilateral infradiaphragmatic vagotomy to subtotal gastrectomy produces a higher percentage of achlorhydrias than has

TABLE V.—*Early Follow-Up Results—4 months to 28 months*

	Gastrectomy		Gastrectomy-Vagotomy	
	No. of Cases	%	No. of Cases	%
Well	38	83%	34	85%
Improved	7	15%	6	15%
Unimproved (jejunal ulcer)	1	2%	0	0%
	46	100%	40	100%

been attained by any other medical or surgical therapy. It must be remembered, however, that many of these test meals were performed soon after operation and it is possible that there may be significant changes in subsequent studies.

In the evaluation of follow-up results, it is important not only to establish the presence or absence of jejunal ulceration, but also to determine whether there are any distressing symptoms attributable to altered gastric function. Eighty-six patients were personally interviewed four to 28 months after operation. They were specifically questioned about pain, bleeding, vomiting, diarrhea and evidences of the dumping syndrome. In the few cases in which these symptoms were present, they were usually mild.

Most patients in both groups experienced some post prandial fulness or distress for a short period after operation. However, this was mild and transient. Two patients in each group complained of pain characterized by fulness, epigastric oppression, and occasionally cramps. In addition, one had typical ulcer pain, which was accompanied by bleeding 11 months after subtotal gastrectomy without vagotomy. He was treated conservatively for a jejunal ulcer, and for the past few months has been well.

Comparison discloses that occasional vomiting was more frequent in the gastrectomy group and a mild diarrhea more common in the gastrectomy-vagotomy group. An interesting finding in the latter group was the frequent relief of habitual constipation.

The dumping syndrome was seen in only one patient in this series. This occurred after subtotal gastrectomy with vagotomy. The symptoms, however, have become progressively milder during the past year.

On the basis of follow-up observations, these patients were classified as well, improved or unimproved. (Table V.) In the gastrectomy group, in which 46 patients were followed, 38 were well, seven were considered improved but not entirely well because of the presence of one or more of the symptoms previously described. The one patient who developed a jejunal ulcer was considered unimproved.

In the gastrectomy-vagotomy group, 40 cases were followed; 34 were well and six were improved.

DISCUSSION

The addition of infradiaphragmatic vagotomy to subtotal gastrectomy in this group of patients has not caused any mortality but has added to the immediate postoperative morbidity. The reaction to operation was somewhat more severe, and the pulmonary complications were more frequent. While gastric atony is a common complication after vagotomy alone, its effects are minimal when subtotal gastrectomy is performed simultaneously. Gastric retention and postoperative vomiting were infrequent and mild in both groups. Severe diarrhea was not seen in this series, and a mild diarrhea occurred with the same frequency in the two groups during the early postoperative period. Subsequently loose bowel movements were more common in the gastrectomy-vagotomy group.

Abdominal distention was not seen frequently in either series, and could not in any case be attributable to the vagotomy. The substernal pain following infradiaphragmatic vagotomy occurred in four of the 46 cases and was never very disabling or prolonged.

Acid secretion studies indicate that the combined procedure favors the production of an achlorhydria, the presence of which, in our experience, precludes the development of recurrent ulcers.

Follow-up studies have revealed that the differences in symptomatology in the two groups were not significant. One jejunal ulcer was diagnosed clinically in the gastrectomy series, but it is too early to draw conclusions regarding the ultimate recurrence rate in either group.

SUMMARY

1. Theoretically, subtotal gastrectomy with bilateral infradiaphragmatic vagotomy should diminish the incidence of jejunal ulcer.

2. The addition of vagotomy to subtotal gastrectomy in this series did not cause any mortality.

3. The combined operation resulted in an increase in the immediate postoperative morbidity.

4. The disabling symptoms of gastric atony commonly seen after vagotomy alone were not present when the combined operation was used.

5. There is a higher percentage of achlorhydrias following the combined procedures than with subtotal gastrectomy.

6. Future follow-up observations in these groups will determine whether subtotal gastrectomy combined with bilateral infradiaphragmatic vagotomy will lower the incidence of jejunal ulcer.

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DISCUSSION.—DR. LESTER R. DRAGSTEDT, Chicago: I am somewhat surprised that Dr. Colp and his associates have apparently been unable to secure satisfactory results in the treatment of peptic ulcer by vagotomy alone or by vagotomy combined with gastroenterostomy, in those cases that have obstruction at the pylorus. In our clinic this operation has made its way until at the present time all the surgeons in our hospital prefer the operation of vagotomy alone or vagotomy plus gastroenterostomy to subtotal resection.

Up to this time a total of 430 of these operations have been performed and we are all agreed that the results are more satisfactory than we have seen from subtotal gastrectomy. It would seem to me that a combination of the two procedures is unwarranted at the present time. I feel certain that a large number of patients will lose an important digestive organ unnecessarily. The great majority of these patients can be cured, and will stay cured for a long period of time, if vagotomy alone is done. It is true that postoperative management is a little more difficult with vagotomy alone than if the operation is combined with gastroenterostomy. That is due to the necessity for controlling the postoperative decrease in tonus and motility of the stomach. In our clinic, however, we are successful in doing this, and at the present time we have no difficulty on this score.

I should like to recommend that greater attention be paid to postoperative management when vagotomy is done, and to remind you that the results now secured in the treatment of peptic ulcer by subtotal gastrectomy are much better than when this operation was first introduced, before surgeons had become well acquainted with the technic of the procedure and the technic of postoperative management.

DR. OWEN H. WANGENSTEEN, Minneapolis: I should like to speak of a new indication for gastric resection for ulcer disease. Before doing so, however, I wish to comment briefly on one item in this discussion, viz., the value of vagotomy as an auxiliary procedure in an operation which of itself is not adequate to thwart the threat of recurrent ulcer. Accumulating evidence suggests that a vagotomy must be complete, as Dr. Dragstedt has suggested, or there will be no effect from the vagotomy. Moreover, a complete vagotomy, even in experienced and practiced hands, appears to be difficult to achieve consistently. Vagotomy does provide definite protection against

ulcer both in patients and against the histamine provoked ulcer in the dog. Dr. Dragstedt ascribes this protection to reduction of gastric acidity; my associates and I are inclined to believe from our studies concerning the nature of the protection obtained by vagotomy against the histamine provoked ulcer in dogs, that it is owing largely to delay in gastric emptying. In other words, converting the human or the dog's stomach into a rabbit-type of stomach, in which food is always present, in itself affords considerable protection against ulcer. When, however, gastrojejunostomy or a small gastric resection is added (25 to 33 per cent), the protective action of the vagotomy against the histamine provoked ulcer seems to disappear. It is unfortunate that we do not have a critical objective test against which the protective action of vagotomy can be assessed. The resolution of the efficacy of an operation by clinical trial is not a promising prospect; witness how long it took us to decide that gastrojejunostomy was an unsatisfactory operation for ulcer.

In the first Book of Samuel, we read of Saul, who went in search of his father's asses and found himself a king. Now there are those who profess to go in quest of a king and find asses instead. In "The Three Princes of Serendip" Horace Walpole invents the designation serendipity to indicate finding something not sought after. Such is the nature of the windfall which befell me when I undertook on the first Sunday in September, 1939, to do an emergency gastric resection for a patient with massive hemorrhage from a bleeding duodenal ulcer. The patient had been dilated more than 100 times for a coincidental esophageal stricture by Dr. N. Logan Leven of our Department of Surgery. We had expected fully to have to continue dilating the patient's esophagus interminably, but much to our amazement, it soon became apparent that no further dilatations were necessary. In the intervening nine years, gastric resection has now been done in six such cases with startling results. One of these is a recent patient who carried a gastrostomy for eight years because he could not swallow his saliva. He too had a coincidental duodenal ulcer. A year has intervened now since gastric resection was done in a boy aged 17, for a stricture of unknown origin beginning in the mid-esophagus. He has remained well and swallows solid food of every kind. Prior to operation he could swallow only liquids. In another patient with a congenitally short esophagus and a corkscrew like stricture of the lower esophagus, four years have elapsed since gastric resection was undertaken. She too had submitted to approximately 100 dilatations of the esophagus prior to operation. Two dilatations were done during the early months of convalescence and more have been necessary since.

These patients usually have a good deal of free Hcl in their gastric secretion. Moreover, Dr. Leven and I are inclined to believe, in consequence of this experience, that esophagitis or esophageal stricture is essentially a manifestation of ulcer disease. Moreover, the squamous epithelium of the esophagus is more susceptible to injury by the acid-peptic digestive juice than is the gastric mucosa. Duodenal ulcer is the most frequent variety of ulcer—only because the duodenum is the sole exit for the gastric contents. If the esophagus were the exit for the stomach, rather than the duodenum, every person probably would have esophagitis or acid-peptic ulcer of the esophagus because of the low threshold of resistance of the esophagus to digestion by the gastric juice. Both in the rat and in the pig, in which animals there is a ring of squamous epithelium in the stomach about the esophageal aperture, when histamine is given, ulcers occur regularly in the proventriculus (area having esophageal epithelium) and not in the glandular portion of the stomach.

An undisciplined imagination may be as dangerous as a roving eye. Nevertheless, it is difficult to escape the impression that cardiospasm and eye strictures too may be kept active by the regurgitation of the irritating acid-peptic digestive juice. In any case, I feel justified in exploring the possibility. So far one patient with cardiospasm of long standing has been subjected to gastric resection and with considerable im-

provement. In any case, I feel justified in suggesting that esophagitis and esophageal stricture may be manifestations of ulcer disease and may be relieved by an effective gastric resection.

Dr. Ralph Colp, New York (closing): I want to thank Dr. Dragstedt and Dr. Wangensteen for their discussion. Subtotal gastrectomy as the procedure of choice has been used in our clinic for about twenty-five years. We are satisfied with the procedure. What worries us is the incidence of recurrent jejunal ulceration. As you know, we have the class of patient who has been subject to stress and strain, and therefore if we could eliminate the psychic phase of gastric secretion by infradiaphragmatic vagotomy, we thought perhaps we might diminish the incidence of jejunal ulceration by combining it with subtotal gastrectomy. We are rather reluctant to give up this procedure, although we know there are innumerable clinics now which are performing vagotomy as a solitary procedure, or combined with gastroenterostomy. As a matter of fact, I think this question will be solved within a reasonable time, because at the last review made by the American Gastroenterological Association, there were about 8000 vagotomy cases already done. So that within a period of five or ten years it is possible that we will know whether this simpler procedure will cause us to discard subtotal gastrectomy. After all, none of the operations we are doing for ulcer are ideal. An ulcer of the stomach is in the same category as subtotal thyroidectomy for hyperthyroidism. If the secretion of acid—which is certainly a potent factor in the genesis of ulcer but not the sole cause (because there are innumerable patients with hyperacidity who never develop an ulcer)—could be controlled medically, all these procedures we are doing at present will probably go into the discard.

THE RESPONSE TO VAGOTOMY IN IDIOPATHIC ULCERATIVE COLITIS AND REGIONAL ENTERITIS*

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I. INTRODUCTION

AS ONE OF US REPORTED three years ago,[1] a study of experience with idiopathic ulcerative colitis at the University of Minnesota Hospitals for the 10 years ending January 1, 1944, revealed that the 57 patients treated expectantly and nonsurgically throughout, or until the situation had deteriorated to a point at which the outcome was hopeless before involving surgery, suffered a 28 per cent hospital mortality. On the other hand, the 25 subjected to elective ileostomy at a time when there was a reasonable choice suffered an 8 per cent mortality. Follow-up studies are incomplete, but show that more than half the survivors of expectant therapy from 1934 to 1936 were dead in 1946, while the great majority of those subjected to ileostomy in the ten-year period were living and well. Cancer in the remaining colon took a high enough toll to establish a policy of subsequent colectomy in all who needed ileostomy.[2]

In the period from 1944 to the fall of 1946, nearly all patients with ulcerative colitis were subjected to surgery, the hospital mortality remained below 10 per cent, and most patients returned to a nearly normal life. The utilization of a program of ileostomy, followed by colectomy with or without ileoproctostomy, thus was successful in terms of survival. On the other hand, it suffered from many disquieting facts. It was a confession of defeat in that nothing was done to salvage the diseased bowel, relying on removal of this bowel instead. It inflicted radical and somewhat deforming surgery on patients usually already somewhat emotionally unstable. It was not entirely free of annoying complications such as skin erosion and ascending ileitis. There was also the occasional catastrophe, no less disturbing because several occurred before surgery.

The need for a therapeutic method which might salvage the colon and avoid the extensive surgery was obvious. As recounted elsewhere, various members of the University Hospitals Staff have employed folic acid,[3] tetraethyl ammonium bromide,[4] and propyl thiouracil as suggested by Laurence Martin.[5] Employment of sulfathaladine[6] and of oral streptomycin seemed only rarely to help.

Employment of division of the vagus nerves was precipitated by a 20-year-old girl who had previously had all her colon and 5/6 of her ileum removed

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for colitis and ascending enteritis. Severe involvement of the remaining bowel failed to respond to all known conservative measures. Vagotomy was performed in October, 1946, at the suggestion of Dr. C. J. Watson of the Department of Medicine at the University of Minnesota. This procedure plus revision of ileostomy resulted in striking improvement. Other procedures have been required, but the patient maintains her weight and fair health at the present writing.

This result prompted us to employ vagotomy in four patients without other surgical therapy, all with mild disease, and to follow the group for six months before making the decision to use the procedure more extensively. At the end of this period, three of these patients presented normal proctoscopic findings, and the fourth was reported as "healed ulcerative colitis." All four had formed stools not oftener than twice a day.[7]

II. PLAN OF STUDY

A more extensive study seemed imperative. The clinical studies were carried out by the present authors. Experimental animal work was performed by Lillihei, Dixon, Friesen, and Wangensteen, and is being separately reported by them.[8]

The plan of clinical study was formulated in an effort to evaluate every factor which might give some clues as to the mechanism of the effect and as to the selection of those cases which might benefit most by the procedure.

One week was employed for each series of studies. Such a series was prosecuted before surgery in those patients considered in condition to tolerate it, and again about a week after vagotomy. Patients were similarly re-studied every three months when possible until we were satisfied of the completeness of the division and the healing of the process. Thereafter patients have been seen less frequently, and the studies have been usually less varied.

Each series of studies included proctoscopic and Roentgen barium enema examination, a three-day observation with recording of size, consistency, and frequency of stools, laboratory checks of stools, transit time through the intestinal tract as measured first by charcoal ingestion, and later by barium meal and close following fluoroscopically, electrocardiograms, triple histamine gastric analysis,[9] 12 hour overnight gastric collection,[10] and Hollander insulin gastric analysis.[11]

III. GENERAL MANAGEMENT OF PATIENTS

Many of the patients came to the University Hospitals in deteriorated or critical condition. One was transferred in hepatic failure and died before surgery could be considered in spite of vigorous therapy by both the Medical and Surgical services. This patient is not included in the series. One refused surgery and died six weeks later elsewhere. Because of the small reserve of these patients emphasized by these cases, all in the series were carefully prepared before embarking on surgery.

High caloric preparation is difficult in these cases, as increased feeding

has resulted in increased diarrhea, with water, salt, and protein loss. In many, therefore, preparation by the intravenous route has been necessary. Blood, plasma, and 10 to 20 per cent glucose solutions have been generously employed. We have customarily added insulin directly to the 15 or 20 per cent glucose in the amount of one unit to four grams, a measure which usually keeps the urine sugar free and the blood level in a normal range. By the use of the polyethylene tubing recommended by Grindlay,[12] it has been possible to deliver these concentrated sugar solutions directly into the superior vena cava by inserting 40-50 cm. of tubing through the antecubital vein; such a combination permits administration of 400-500 Gm. of glucose per 24 hours, and the same tubing has been employed as long as two weeks.

The employment of a long tube for suction in the terminal ileum has been employed several times in the past five years. It seems to have helped in preparation of some of the sickest cases, but unlike Grier Miller,[13] we have not been successful in keeping the colitis quiet except by oral starvation in addition to low ileac suction.

As previously reported, the early experience was that 30 per cent of patients with ulcerative colitis developed thrombosis or embolism in association with the performance of ileostomy; the routine administration of a single oral dose of dicumarol the night before surgery, however, resulted in a series of 20 consecutive cases with no thrombotic complications.[14] In the vagotomy series, after 20 cases without proplylaxis, embolus has occurred once. The patient recovered on anticoagulant therapy. The present plan, therefore, again calls for 200 mg. of dicumarol the night before surgery.

In cases requiring extensive intravenous preparation, it is now the practice to add heparin prophylactically to the infusion at the rate of 30-40 mg. every four hours.

The anesthesia to be employed is the choice of the anesthetist. We use extensively and with complete satisfaction a mixture of pentathol (25 mg/cc) and curare (five units/cc) intravenously, supplemented by a mixture of equal parts of nitrous oxide and oxygen by an intratracheal tube.[15] The intravenous infusion is given either through the cubital or the external jugular vein; the saphenous is never employed, for fear of thrombosis.

Our vagotomies have usually been performed through an incision in the left anterior seventh intercostal space. At the beginning of the study, a segment of the eighth rib was removed, but this resulted in excessive pain. The intercostal incision, with electrocoagulation of the exposed intercostal nerve, has left little postoperative discomfort. Omission of all sutures in the intercostal bundle seems also to have helped. Closure is accomplished with No. 2 chromatic catgut encircling the seventh and eighth ribs, and precise fine silk (1¼ lb. test) approximation of muscles and skin.

We routinely infiltrate the mediastinum with 10 cc. one per cent procaine before working in that area, a procedure resulting from one occurrence of cardiac arrest.

Postoperatively, gastric suction is now employed for one to two days, food thereafter being taken for a few days only as the patient hungers for it. Ambulation begins the day after surgery.

In seven patients, ileostomies had been performed in line with our former program, before vagotomy was employed. In one the ileostomy was closed at the same sitting, in another six weeks later. In the others it was learned that the ileostomy must be widely patent if static difficulties are to be avoided, as an intestine capable of overcoming moderate stenosis at an ileostomy becomes unable to do so following division of the vagi. One ileostomy made after vagotomy, with this in mind, has given no static difficulties.

It has been observed in several patients that the days immediately following vagotomy are marred by a profuse secretion of thin fluid from the intestine. This is not a serious problem except in the presence of a high ileostomy. In such cases the ileostomy drainage may exceed ten liters a day for several days. A sharp watch must be kept daily on serum sodium, potassium, and chloride levels, on the carbon dioxide combining power, and on the weight of the patient, and aberrations must be appropriately corrected at once. It is best to permit only soft or solid food by mouth, and to supply the fluid replacement only by the intravenous route.

IV. CLINICAL RESULTS OF VAGOTOMY

As reorted in the preliminary papers,[7, 16] most of the clinical results have been very encouraging, as the following case summaries indicate:

Case 1. A 23-year-old University student (777589) was admitted May 1, 1947, because of acute onset of abdominal pain. There was a history of resection of the terminal ileum and colon to the apex of the sigmoid and ileosigmoidostomy as a staged procedure three years earlier. He had been well in the interval, having two to three stools daily. Examination showed a very active proctitis and sigmoid colitis, a tender, spastic abdomen, a temperature varying from 100° to 104° F. Perforation of the remaining sigmoid colon seemed most likely on the basis of ausculatory and Roentgen findings. A long Wild[17] tube was placed in the small bowel, and penicillin, streptomycin, blood, and glucose were appropriately given. He was explored May 4, it being felt the perforation should have sealed in that time. In addition to the matted fresh adhesions and violent peritoneal reaction anticipated, the top two feet of the eight feet of free small bowel was found to be involved in a severe inflammatory process interpreted as regional enteritis. A double barreled ileostomy was done as low as possible.

His course thereafter was gratifying, and he went home May 22. Readmitted June 10 with dysfunction of the ileostomy and cramps which led to a diagnosis of extensive enteritis above the ileostomy. Proctoscopy showed almost complete healing, especially in the rectum. He was starved by mouth and fed formula into the distal ileostomy in preparation for surgery. On June 26 a transthoracic vagotomy was done, and at the same sitting the ileostomy and enough bowel to confirm the diagnosis were resected, and end-to-end anostomosis was done in thickened, angry looking ileum. The postoperative course was uneventful except for recurring pneumothorax which required repeated aspiration. Dismissed July 11, the patient gained 12 pounds the first week at home, 30 pounds the first month. He has remained well, has married, and works as an engineer six days a week. He has two small stools a day more formed than at any time since onset of his colitis.

Case 2. A six-year-old boy (763487), with a ten month story of bloody diarrhea, was admitted February 26, 1946. After diagnostic studies, a single barreled ileostomy was performed March 7. About 10 days later he developed evidence of dysfunction of the ileostomy in association with a flare-up of discharge from the colon. After a long try with conservative methods, he was re-explored April 30 and adhesions of omentum and ileum to transverse colon were freed, relieving ileac obstruction close to the ileostomy. Further trouble with the ileostomy led to resection of the ileostomy and 33 cm. of ileum, with a pathological diagnosis of ulcerative ileitis. Because of persistent active proctitis he was vagotomized on August 21, 1947. Repeat proctoscopic examination on September 16, 1947, showed total absence of the granularity, friability, and bleeding seen four weeks earlier, and the mucosa was described as normal. The ileostomy was closed September 18. This patient has gained weight and strength, goes to school without limitations of diet or activities, and has one or two formed stools daily. Proctoscopic examination March 5, 1948, showed normal bowel. Miscroscopic examination of the stool shows no pus, and there is a trace of blood on the benzidine test.

Case 3. A 19-year-old boy (781510) was transferred from another hospital on September 2, 1947, with a six-week story of high fever, abdominal cramps, and diarrhea running to 12 stools a day. He weighed 112 pounds, in contrast to his usual weight of 152 pounds one year before. He was emaciated but had been freely transfused. Films from the other hospital showed diffuse acute enterocolitis, with classical "string sign" in several places from jejunum to colon as well as colitis. Oral feeding seemed out of the question; after two days of 15 per cent glucose and blood by vein, a transthoracic vagotomy was done. Penicilin and streptomycin were given the first few days. The patient had no stools the first four days after operation, and was given mineral oil, following which liquid stools appeared until September 14, when formed stools appeared. He has had one or two formed stools a day since that time, except for three occasions of one day of diarrhea. He gained 35 pounds in the first three months and is again a student at the University.

Despite such striking cases the vagaries of idiopathic colitis cause us to draw conclusions only with misgivings. That many other factors than the division of the vagi may have played a part in our results can be emphasized by one case:

Case 4. A 47-year-old woman (778555) was admitted from another hospital on February 14, 1948. She had had mucous colitis for 20 years, with superimposed acute ulcerative colitis of two months' duration, diagnosed proctoscopically, which had depleted her hemoglobin and serum protein stores. Oral feeding was totally inadequate and tube feeding not tolerated. A polyethylene tube was placed on February 22 into the superior vena cava through the right antecubital vein, through which one liter of 20 per cent glucose covered by insulin was given daily. Blood and plasma were given in other veins. She developed recurrent deep femoral thrombophlebitis which was treated by heparin. She took no food by mouth until after removal of the polythene tube on February 28. She regained strength rapidly in the next few days. Proctoscopy on March 3, 1948 showed normal mucosa. The patient has had one formed stool a day since that time. Vagotomy was not done because of a left eventration of the diaphragm, deep phlebitis, and complete anatomical recovery from her only attack, which had been heralded by extreme emotional strain not likely to recur.

There have been four deaths in the group of patients for whom vagotomy had been planned or was actually performed. The first occurred in a woman who was admitted in acute hepatic failure and who died in coma despite our efforts to prepare her for surgery. The second was a 32-year-old patient who had had colectomy and ileosigmoidostomy four years earlier. As the mediastinal pleura was being opened to perform vagotomy for recurrent proctitis,

cardiac arrest occurred. It was converted to fibrillation under massage and then to normal rhythm by intraventricular procaine injection. The vagi were not divided. She died, apparently of ventricular fibrillation, eight days later.

Our third death occurred as follows:

Case 5. A 32-year-old housewife (UH 776892) has ileostomy performed on 4/21/47 as a desperate final gesture for a very active generalized colitis. She had had elective gynecologic surgery elsewhere eight months earlier despite the colitis. Following ileostomy she regained strength and was allowed to go home. She returned on 10/9/47 with abdominal cramps and profuse bloody purulent drainage from the rectum. Transthoracic vagotomy was done 10/28/47. She did not respond well, although the rectal drainage did decrease. Gradual decline followed, and she died in hepatic failure, 1/15/48. Autopsy showed remains of a very old abscess involving the sigmoid colon and three segments of ileum proximal to the ileostomy, with a large fistula into each, and acute liver atrophy. The fistulas were thought to antedate ileostomy.

This woman might not have died if we had attacked the bowel when her condition was fair. Although one barium enema examination has been since re-interpreted to show an ileosigmoid fistula, this situation was not recognized during life, as it might have been if we had not employed transthoracic vagotomy.

Our fourth death appears to have occurred from other causes:

Case 6. A 27-year-old man (UH 780469) was admitted 8/12/47 with a seven year history of colitis. His home physician had already performed ileostomy and colectomy, leaving a rectum which was involved with active proctitis. His course had been complicated by repeated bouts of ileac obstruction for which he had had two explorations with enterolysis. The patient had a burning desire to have the ileostomy closed, and vagotomy was hesitantly suggested and accepted only because it offered some hope in this direction. We considered combining enterolysis, revision of the ileostomy, and subdiaphragmatic vagotomy, but there were numerous stitch abscesses in the several abdominal scars. After transthoracic vagotomy, the rectum showed some improvement before dismissal. The patient refused to return for follow-up because of resentment against use of gastric analyses. Recurrent bouts of obstruction occurred some months later. A strangulation obstruction was surgically relieved by the home physician on one occasion. He died following another exploration for recurrent obstruction at a third hospital in April, 1947. The rectal discharge is reported by his home physician to have decreased considerably in the last few months.

Twenty-eight cases comprise the series on whom vagotomy has been performed. Two were done through abdominal incisions, one to exclude the diagnosis of carcinoma of the sigmoid colon after barium could not be pushed past this point, the other because of an old subscapular abscess. The others have been done transthoracically to avoid all possible manipulation of the colon. One patient had had only a functional diarrhea (12x daily) for four years without demonstrable pathologic changes. She has had an excellent result, now usually having one or two formed stools a day. Two vagotomies for colitis are too recent for full evaluation and are not included; both show mucosal improvement.

Therefore, 25 cases of vagotomy on patients with ulcerative colitis are available for follow-up consideration. In 16 of these, vagotomy was the only surgical procedure (see Table I). Six of these latter have become asympto-

matic, i.e., they have no more than two stools a day, the stools are soft formed and free of gross blood, pus, and mucus, and they have no gastric distention or abdominal discomfort.

Four of these 16 cases are not asymptomatic but are improved; one of these is so listed because she was committed to a State Hospital and there

TABLE I.—*Clinical Results of Vagotomy in Ulcerative Colitis and Enteritis*

	Asympt.	Improv.	Not Improv.	Worse
Vagot. alone	6	4	5	1[1]
Vagot. with ileost.	3[2]	3[3]	—	1[4]
Vagot. with previous anastomosis	1[5]	—	1[6]	—
Totals	10	7	6	2

1 Required emergency ileostomy after barium enema three months later.
2 One had both sigmoiditis and high regional enteritis; the ileostomy was closed at the same sitting. One had enteritis above the ileostomy. One had high enteritis and proctitis; the ileostomy was closed in four weeks, at which time the rectum had healed.
3 Two had high enteritis; one proctitis.
4 Died at three months of multiple fistulization from high ileum to sigmoid thought at autopsy to pre-date surgery.
5 Massive hemorrhage from enteritis above ileoproctostomy.
6 Previous ileoanal "pull through" with diseased ileum.

has been no success in gaining information as yet; there had been reduction in stools in the first two weeks. This woman was seen in June, 1948, and is symptom free. Another is continuing to improve, but the period of observation is only nine weeks. A third is showing progressive roentgen-ray and clinical improvement at 18 months; the proctoscopic appearance is normal. The fourth has had improvement in symptoms and loss of most of the inflammatory polyps in the colon, but still has occasional days with as many as four stools.

The disease may be classified according to the type of involvement. As Bargen has pointed out, there may be maximal involvement in the rectum with apparent spread from this area to the rest of the colon, and perhaps to

TABLE II.—*Type and Extent of Disease in Patients Subjected to Vagotomy*

	——Universal Colitis——		——Regional Colitis——	
	Number of Cases	Percent Improved	Number of Cases	Percent Improved
Ileum involved	10	70	4	100
Ileum free	10	60	1	0

the ileum, the universal type, or the segmental or regional types of colitis or enterocolitis, of which regional enteritis is a sample. Twenty of the 25 cases were universal in type, and about half of all the cases had ileac involvement. There seemed to be no definite relation between the type and extent of disease to the response to vagotomy (Table 2).

Five of the cases subjected to vagotomy alone are unimproved. One 12-year-old boy had *endameba histolytica* in the stool; he has two to three stools a day when he can be kept from popcorn and peanuts. Another is an extremely uncooperative and high-strung boy of 17 who came with 18 stools

a day and is now down to nine; he is listed as improved but has refused to return for evaluation. Two patients were well for many months only to suffer a recurrence of diarrhea.

One patient who had vagotomy performed to control massive bleeding progressed well for three months only to suffer recurrent activation requiring emergency ileostomy.

Nine patients who had had ileostomy or some form of ileoproctostomy were subjected to vagotomy. This was done for relief of higher regional enteritis or ascending enteritis in five cases, for proctitis in one case, for recurrent colitis in one, for involvement just above a low ileoproctostomy in one, and for involvement of ileum previously used for an anal "pull through" in one.

The last case mentioned is unimproved; he still presents actively diseased ileum on proctoscopy, although the stools are nine instead of 15 to 18 daily. The one who had vagotomy for an exacerbation after ileostomy is the third death listed above.

Three of our patients have suffered recurrent bouts after vagotomy.

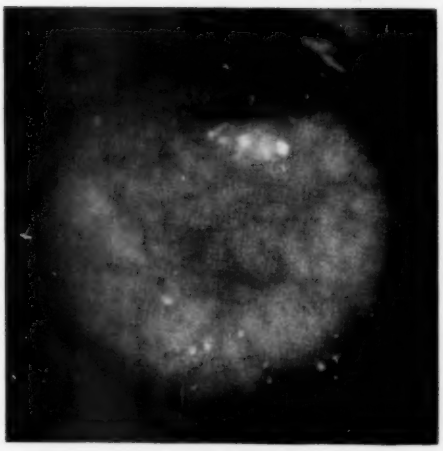
Case 7. A 47-year-old woman (620076), with colitis dating from 1933, came to us December 5, 1946. She had had spells of diarrhea and cramps twice a year for years, with vomiting and distention. These bouts lasted two or three days, but distention and abdominal discomfort were never entirely absent. Proctoscopic examination showed moderate low-grade involvement most marked in the rectum. Barium enema showed nothing abnormal except some mucosal changes in the low sigmoid. Following vagotomy she suffered diarrhea for a few days, then enjoyed normal bowel function and presented a normal proctoscopic picture until May, 1948, when she developed two or three stools a day, liquid half the time. No abdominal discomfort was noted. No gross blood or pus was seen in the stool. Proctoscopic examination shows only very slight hyperemia. Barium enema shows only the slight atony usually seen after vagotomy. Bland diet suggested.

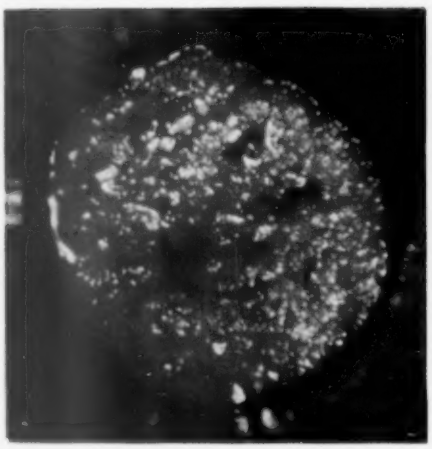
Case 8. A 32-year-old woman (782759), with colitis the preceding two years, was admitted October 28, 1947, because of massive hemorrhage and shock. This was treated expectantly and subsided. There were then two to four liquid to soft stools daily. Study showed involvement of the rectal mucosa of moderate degree, and loss of haustration of the entire colon. After vagotomy her stools returned to normal consistency and once daily, and the proctoscopic appearance became almost normal. Follow-up studies in early March, 1948, showed active disease in the rectum. Unfortunately a barium enema was performed at this time. A severe exacerbation occurred during which the situation became so critical that an emergency ileostomy was performed. Recovery thereafter was slow, but progressive.

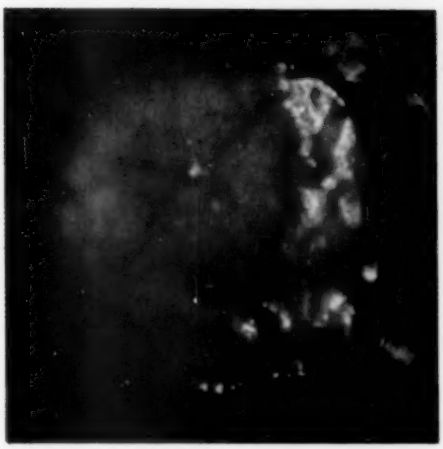
Case 9. A 56-year-old woman (670169), with colitis dating from 1933, came to us September 21, 1947. She had had two to three formed or liquid stools daily for years. She had been subject to severe bouts of bloody diarrhea and abdominal cramps and fever, coming in the early summer each year. She presented an active proctititis with pus and mucus present. Roentgen study showed moderate colitis and low ileitis. After vagotomy she slowly improved, and in December, 1947, was having one formed stool a day, presented a normal roentgen study on the colon and much improved proctoscopic appearance. About March 15, 1948, she began to have four to five liquid stools a day, with extreme urgency. This bout is less severe than before vagotomy, and is not accompanied by abdominal discomfort. Examination May 18, 1948, shows active ulcerative colitis involving the upper

A

B







C

D

PLATE I.—Photographs of the rectosigmoid mucosa in ulcerative colitis.

A. Same patient as Figure 1, before surgery.

B. Same patient six weeks after vagotomy.

C. Patient 784756, a 17-year-old girl with a two-year history of colitis, before surgery.

D. Same as C, three months after vagotomy. The patient had gained 30 pounds.

rectum and lower sigmoid. The patient was symptom free and the protoscopic appearance normal in July.

Weight. The average weight gain from the time of vagotomy to the present is 15 per cent. One of those gaining best is classed for other reasons as unimproved. Maximal weight gain occurred in a 24-year-old boy with a seven-year history of colitis and a very spastic, rigid colon. His weight rose from 39 Kg. to 64 Kg. in the three months after vagotomy. He is asymptomatic.

Proctoscopic changes. Proctoscopic changes could be evaluated in 20 cases. In four there were no abnormalities here at any time. In four more, an actively diseased mucosa has assumed a normal appearance. In seven there is definite improvement without complete healing. In two, definite disease in the rectal mucosa has remained unaltered. In three cases the mucosa looks more diseased than before vagotomy; two of these are in exacerbations occurring after the procedure.

The majority of those patients who had diseased rectums present at examination have shown definite improvement in the proctoscopic appearance within two weeks after vagotomy. In most, this improvement continued over a period of months, being particularly slow in those with long-standing colitis or with marked fibrosis.

Some of these changes were very striking, as shown in Plate I.

Roentgen changes. In all but one of those cases in which abnormal roentgen findings were present initially and in which serial barium enema roentgen studies were possible, improvement followed vagotomy. There was only one instance in which the appearance returned entirely to normal; this patient (670169) developed an exacerbation six months after vagotomy. In one case, spasm appeared to be more marked in the colon after vagotomy than before (782759). This patient later suffered an exacerbation also.

In general, improvement has been progressive to such a degree that a status approaching normal is ultimately to be anticipated. Such a change is indicated in the roentgenograms of Figure 1.

There was throughout the series a tendency toward less spasm after division of the vagi. This tendency was also observed in a group of patients vagotomized for duodenal ulcer at the Minneapolis General Hospital.

Stool studies. Stool studies have included repeated search for *endameba histolytica*, pus, and mucus by the microscope, and for blood by the benzidine and guaiac tests. Blood, pus, and mucus have been found with less frequency after vagotomy in half the cases, but there are none free of all these constituents. Absence of gross blood, pus, and mucus has seemed usually to follow operation.

Retention. Gastric retention required later gastroenterostomy in one case. One or two others complained of bloating and sour eructation for a short time only.

V. RESULTS OF SPECIAL STUDIES

Gastric acids. Triple histamine (Lannin) analyses were changed by vagotomy more than expected on the basis of the studies of others,[18, 10] in

A B

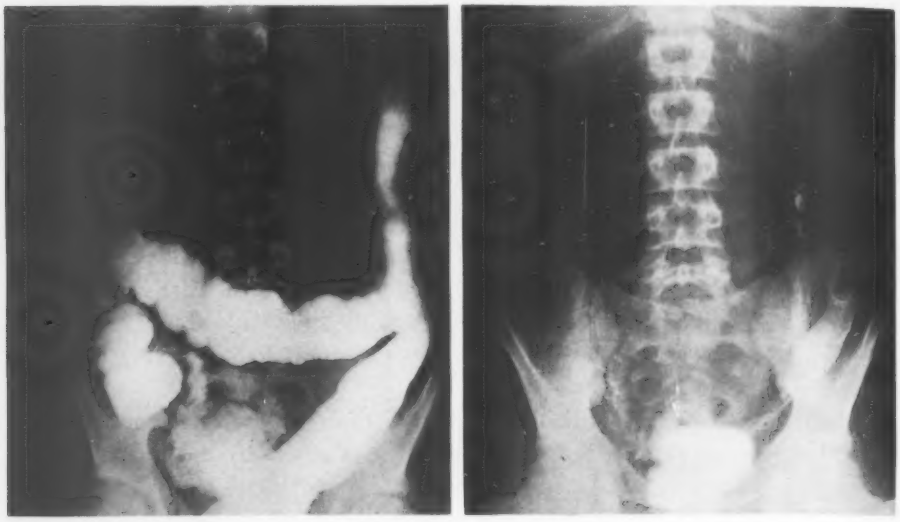


FIG. 1.—Barium enema Roentgenograms of case 784831—an 18-year-old boy with a three-year history of colitis. (a.) Filled colon prior to surgery. (b.) Evacuation film prior to surgery.

C D

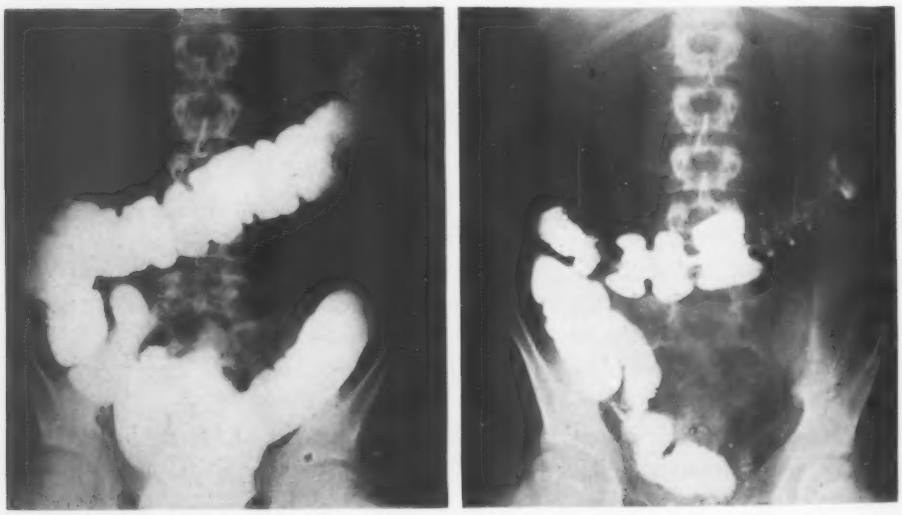


FIG. 1.—(c.) Filled colon eight weeks after vagotomy. (d.) Evacuation film after vagotomy.—Note decrease in spasm and return of haustral and mucosal markings. The patient had gained twenty pounds in this period.

that three patients became totally achlorhydric. Other than these, there was little change except for a moderate tendency to reduction in the free acid response.

Our results with the 12-hour overnight collection used by Dragstedt suggests that the large preoperative volumes seen by him were related to the gastroduodenal ulcer picture. The mean preoperative volume was 440 cc., with no free acid in two-thirds of the cases. The mean postoperative value was 210 cc. with no free acid in a slightly higher fraction.

The Hollander insulin gastric analysis was performed by giving one-half unit of insulin per kilogram of body weight subcutaneously, collecting gastric juice continuously for two hours, with separation into 15-minute samples. The test was accepted as implying complete division only if there was no rise in free acid with a blood sugar level below 45 mg. per cent. In most instances this was performed two or more times in the postoperative period, and all tests were satisfactory before division of the vagi was considered complete.

The first patient presented evidence of incomplete division, and had the rest of the fibers divided at a second procedure. This did not seem further to improve her status.

Three other patients present unsatisfactory evidence of complete division in that there is an acid response to the insulin test. One had very minimal universal colitis and has been followed for 16 months. Two had regional enterocolitis (one a classical regional enteritis involving high ileum, jejunum, and duodenum, as well as sigmoid). All three are totally asymptomatic. Each of the patients suffering recurrent bouts of colitis presents insulin test evidence of complete division of the vagi (two on one test only, as yet).

Transit times. The time required for transit of material through the intestinal tract has been broken down insofar as possible. It is now common knowledge that there is delay in gastric emptying after vagotomy. An attempt was made to determine whether or not there is a retardation in transit through the small intestine and the colon in these cases.

To study the small intestine, the moment of entry of barium into the duodenum was noted as often as possible in gastro-intestinal stasis studies.* Fluoroscopic follow-up studies were so spaced as to try to estimate the time of entry into the cecum. In only eight cases was it possible to time these occurrences both before and after vagotomy. The mean small bowel passage time was 3.5 hours before operation and 7.5 hours afterward. In no instance did passage fail to be slowed after surgery.

It is recognized that slower emptying of the stomach may contribute to this lessening of speed of passage in the small bowel. As a means of evaluating the intrinsic activity of the ileum, long nasal tubes were passed into the ileum for recording of activity by balloon and tambour. In view of our total failure to pass such a tube out of the stomach after vagotomy, it was left in during

* The authors wish to express their profound gratitude to Dr. L. G. Rigler and his staff for their patient cooperation in the frequently exasperating studies entailed.

the procedure and convalescence for the purpose of repeating the studies after vagotomy. The results are not entirely conclusive as yet, but such observations as have been made suggest reduced tone and activity after section of the vagi.

Transit through the colon was more difficult to evaluate, and in only three instances was it possible to time arrival at cecum and rectum both before and after surgery. The mean colon transit time before vagotomy was 3.1 hours, afterward it was 11.3 hours.

An effort was made to judge intestinal activity by checking the time required to pass six Gm. of charcoal taken orally at 6 P.M. There were 14 cases without ileostomy or resection in which comparisons were made. The relative infrequency of stools in the postoperative observation in most patients distorts the picture in one direction, and the occasional profuse secretion in the other. The means were 18 hours before and 23.3 hours after vagotomy.

Electrocardiographic observations. At first it was thought that persistent changes followed vagotomy, but these appear to be no more common after this than after other procedures.

Laboratory observations. With the observation of striking improvement in the first cases, Lillehei, Dixon, Friesen, and Wangensteen[18] directed the experiments they had already been performing on the origins of colitis toward the possible role of autonomic innervation. They confirmed Lium's[19] finding of usually fatal bloody purulent diarrhea in dogs after removal of the mesenteric ganglia. They found, however, that this effect does not follow if vagotomy is done at the same sitting.

Emotional changes and the rectal mucosa. Wolf and Andrus have reported that intense swelling and engorgement occur in the gastric mucosa of man in the course of strong emotional reactions, such as anger. They furthermore noted this reaction of the mucosa to be lost after division of the vagi. Holman has found that essentially the same responses to emotional reaction occur in the terminal ileum and cecum, and it occurred to us together that the same changes might be studied in the rectums of patients suffering from ulcerative colitis.

That vagal influences upon the sigmoid and rectum exist would at first seem very unlikely. Degeneration studies after division of the vagi in experimental animals indicate that vagal fibers extend only to the midportion of the colon,[22] and that division of fibers in the sacral outflow results in similar degeneration in nerves in the left colon.

The finding of rapid rectal healing after vagotomy for ulcerative proctitis in a patient with ileostomy would suggest some more direct effect than change in the character of the contents coming from above.

Experimental work by Almy and Tulin[23] has shown that severe pain produces increased motor activity in the rectum and that emotional responses produce in some normal people an engorgement of the mucosa and increased secretion.

Thus far, two patients have been studied before and after vagotomy for colitis.

Case 10. A 30-year-old housewife (MGH 1478A-48) presented a seven-year history of colitis, and was admitted in February, 1948, because of an exacerbation and multiple huge abscesses on the back, buttock, and thigh. After drainage of these and dietary and general management, the colitis subsided. Proctoscopic examination, April 28, with the patient comfortable in the Sims position, showed only very minimal engorgement of the moderately granular mucosa when pain was produced by probing and repacking the abscess pockets. Discussion of her sorest subject, prolonged separation from her children, resulted in an immediate tense engorgement of the mucosa, excessive secretion of watery fluid, and in the sudden appearance of four or five superficial hemorrhages on the surface under observation. With change of the topic to other subjects, the engorgement disappeared almost as rapidly as it had come.

This patient was re-examined in the same manner May 12, 1948, four days after subdiaphragmatic vagotomy. At this time there was a periodic color change not noted before vagotomy in this or other patients. Most of the time the mucosa was pale, but every three minutes it became pinker for ½ minute, without engorgement. Discussion of her children and her separation from them produced none of the pre-vagotomy engorgement, and, even on the disclosure to the patient that a large new abscess in the left buttock would require more surgery and a longer stay away from her children, there was no change.

Case 11. A 19-year-old boy (MGH 3345 A-48) with a five-year history was similarly observed. Several items of conversation were each found to be associated with visible emotional disturbance and engorgement of the mucosa. The changes were definite, but less striking than in the first patient. In discussing his relations with his sister, three superficial petechial hemorrhages appeared in addition to engorgement. This patient had active ulceration present at this time.

On May 17, 1948, five days after vagotomy, the mucosa already looked paler, although it traumatized very easily. Review of the above topics of conversation produced no definite changes in vascularity or engorgement. We were not entirely satisfied that he had been as emotionally upset as the first patient or as before surgery.

Five additional colitis patients have been examined in this fashion, but unfortunately the vagotomy had already been performed before such observations were conceived. In three there was definitely no engorgement or color change on discussing subjects known to be very sensitive to the patients. In another there was one definite increase in color, not while on a sore subject and not associated with engorgement. In the fifth there was a periodic blush of the mucosa, unrelated in time to the subjects which bothered the patient.

Two patients subjected to vagotomy for duodenal ulcer were simliarly studied before and after surgery. Engorgement was minimal but definite on discussion of painful subjects before surgery, and absent afterward, although one of the patients showed a periodic pinking not correlated to conversation or pulse rate.

These observations seem definite, even though we appreciate that most of these patients are much less tense and excitable after vagotomy than when they still had pain or other symptoms of colitis or duodenal ulcer.

The gastroenteric reflex. In two patients there was a definite history of urgency to defecate on partaking of food, with relief from this annoying difficulty after vagotomy. This has not been felt to mean abolition of the gastroenteric reflex beyond doubt because the frequency of stools had been so much

reduced by the procedure. Studies on changes in small bowel motility by the inlying balloon method are as yet inconclusive on this point.

VI. PREOPERATIVE ESTIMATE OF EFFECTIVENESS OF VAGOTOMY

Since some of these patients have done very well and others have not, we have critically reviewed all available evidence in an effort to delineate the factors either indicating or contra-indicating employment of vagotomy.

It at first seemed that early cases responded more favorably than those of many years' duration. Charting of clinical results against duration shows no correlation whatsoever.

The degree of fibrosis does seem to play a part. Almost total loss of haustral markings, and of distensibility, both by proctoscopic and by radiological estimates, leads regularly to a poor result. Those with an estimated three-quarter loss of elasticity derived slightly less consistent good results than those with lesser degrees of change. Most of the excellent results were achieved in cases with little or no limitation of elasticity.

This observation has indicated also that patients with marked loss of colic elasticity are slower to improve after vagotomy than those without such loss.

It would seem that the maximal chance of a good end result should be found in those cases vagotomized in the first few weeks of the disease, before fibrosis is a factor.

VII. COMMENT

One of the disturbing aspects of this study is the fear that carcinoma of the colon will develop with the 14 per cent frequency previously reported in old cases on long follow-up. In many cases the bowel has returned far enough toward normal to cause us to hope that this high incidence would no longer prevail. In any case, the present course, with careful observation, seems the only course allowing a solution to the problem.

The mechanism by which vagal section changes the course of idiopathic ulcerative colitis is unsettled. The reduction in colic tone which regularly follows vagotomy would suggest that relief of spasm is important. The rapid response in some cases with ileostomy above suggests the mechanism is not through some change in intestinal juices coming from above. That some change in lysozyme activity is important is suspected by Holman and is now under study by that group.[21]

It is difficult to ignore the possibility that vagal innervation extends as far as the anus; at least the results appear *as if* this were the case. Much of the benefit may then accrue from protection of the mucosa from the reflex effects of the violent emotional stress to which these patients are so subject.

A definite answer to this problem is not possible in the present state of our knowledge.

CONCLUSIONS

1. Idiopathic ulcerative colitis responds favorably in most cases to division of the vagus nerves. Regional enteritis has also responded.
2. The response is usually most marked and most prompt in cases in which there is not great loss of distensibility of the colic wall.

3. Patients with extensive fibrosis in the bowel wall, as a result of colitis, occasionally take many months to improve after vagotomy.
4. The mechanism of this effect is in doubt, but the reduction in mucosal vascular response to intense emotion and the relief of enteric spasm seem to be important.
5. The effect of vagotomy on the vascular response of the rectum to strong emotion is *as if* vagal innervation includes the rectum.

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DISCUSSION.—DR. HENRY W. CAVE, New York: We all know that in ulcerative colitis there is marked disturbance of the motor mechanism of the colon. On the right side of the colon there is hypomotility with resultant stasis and a feeling of fulness in the right side. In the left colon, from the midcolon down, we will say, there is marked hypermotility with marked irritability and resultant diarrhea. Vagal section, as suggested by Dr. Dennis in this excellent presentation, may correct this imbalance. I should like to ask Dr. Dennis the average duration of illness in these cases prior to vagal section. We all know that this disease is a cyclic recurring disease; there is first a stage of acute activity, a second phase of convalescence, a stage of quiescence, and a fourth stage of recurrence of reactivation of the process in the colon. We have seen many cases that have remained quiescent no matter what was done; whether treated medically or otherwise, they have remained quiescent for periods up to two years. I think a good many of Dr. Dennis' cases were of long standing, and it seems to me that where there are irreversible changes with pseudopolypoid degeneration, infiltration in the colonic wall, it is hard to believe that a vagal section can cure that patient of his disease. I am sure when they get to that stage, with thickening, loss of laustral markings, and the disease is irreversible, nothing will do any good except removal, and I want to bring out one particular point in the question of removal of the colon; that is, the question of incidence of malignancy in the colons and rectums that are left in. In our series, seven developed carcinoma. I understand that DR. Cattell at the Lahey Clinic has an incidence of 14 per cent development of cancer in the segment of the colon or rectum left in place. I feel that one is committed to removal of the colon when it gets to the point of possible malignancy on the basis of 14 per cent incidence in the disease.

I should like to ask Dr. Dennis one more question. After vagal section does the temperature subside and does the spasm abate. I think that is important in these cases. As he says, he has been doing the operation only since October, 1946, and the time is too short to evaluate properly the results of his work.

DR. FRANK H. LAHEY, Boston: Anything that can improve our methods of handling ulcerative colitis is certainly welcome to those of us who have to deal with these cases in considerable numbers. It is a distressing disease of unknown origin, unpredictable as to when the acute critical stages arise, and with it there is associated a very definitely high mortality. I wish particularly to compliment the author of the paper on the suggestion that there is another method of treatment to be applied to this distressing disease. I want again to call the attention of this audience to one fact, and I want to be sure that this method does not alter the progress we have made with this disease, and I am quite sure it will not. I would like to say that we must not lose sight of two or three very important things in connection with ulcerative colitis. One is, how quickly an acute stage of the disease can appear and how quickly the patient can die in it. Unless you have seen a large number of patients you may not realize that the disease may become acute overnight, and the patient can die within a week; they can die from intoxication, perforation or hemorrhage.

That again brings up a very important point—when to do an ileostomy. We have had an opportunity to compare two good-sized series of ileostomies in patients with ulcerative colitis. There were 80 cases in each group. The mortality in the first group was 22 per cent; in the last group, in the neighborhood of 5 per cent. That is due to just one thing—the performance of the ileostomy at an early enough date. This is in no way a criticism of the form of treatment; it is a warning lest as the result of delay we get back to the point where we again have a 22 per cent mortality in ileostomies. Another thing we must remember is that when these patients are hemorrhaging from an ulcerating colon they can bleed faster than blood can be put into them and they may require an emergency colectomy. I am particularly

anxious to stress these points lest we delay unduly as we try out this method, but I welcome it as another method of treating this very distressing disease.

DR. C. W. HOLMAN, New York: I should like to summarize our preliminary findings in a patient with ulcerative colitis whom we subjected to vagotomy. We are now rather cautious about interpreting our early findings as a result of this case. The patient was a young man admitted to the hospital because of a large prolapse of the right half of the colon and ileum, following ileostomy performed about a year and a half before. He had had ulcerative colitis for two years prior to operation. In this patient, the large amount of exposed visible bowel provided an excellent opportunity to observe the effect of vagotomy and the influence of various stimuli.

(slides) Before operation you see this prolapse, approximating at times the size of a football. Administration of physostigmine produced hypermotility and slight increase in contractility and vascularity. Dr. Grace and Dr. Wolf found that psychic stimuli, particularly anger, would make the bowel contract and become hypermotile, the vascularity would increase, and at times even ulcerations developed. A transthoracic vagotomy was done, apparently a complete one, as judged from the result of an insulin test. Four days after vagotomy the bowel had lost its motility and no longer responded to psychic stimuli. There was no longer an increase in vascularity. But during the next two weeks this changed, so that eventually he developed increase in motility, increase in vascularity and increase in ulceration as a result of psychic stimuli. Coincidentally, he developed bloody and mucus discharges from the rectum and all evidences of an increase of activity in the lesion of the large bowel. I might say that this postoperative course was complicated by disturbances in motility of the upper gastro-intestinal tract that made feeding difficult, which might very well be a factor in the unsatisfactory result following vagotomy in this patient.

DR. CLARENCE DENNIS, St. Paul (closing): I want to thank all the discussors. The average duration of the disease before vagotomy varied a great deal. The earliest case was done about four weeks after onset of the disease; that is the one with such a good result that I outlined to you. The longest that I can think of at the moment was 14 years; although Dr. Zierold, who is a member of this group has, I believe, a patient who had the disease for 19 years, who had a good deal of improvement only after several months following operation.

With regard to the development of quiescence in the disease after any sort of manipulation, I think it should be borne in mind that this is always a possibility. Dr. Bargen has seen several of these patients with me, and we have discussed them in considerable detail. He tells me he has had two patients with acute ulcerative colitis, on whom he put Boothby masks, with complete subsidence of the disease, and he sent the patient home asymptomatic and with apparently normal proctoscopic findings. He said it looked like a beautiful thing, but never would work again, and it is worth pointing out that this can occur. We have one patient who came in with an acute ulcerative colitis of a few weeks' duration, who was treated with intravenous infusions for a week by a polythene tube in the vena cava, who responded beautifully without surgery and has, at the present time, normal proctoscopic findings and no symptoms.

With regard to Dr. Cave's question about pseudo-polyps, we have only one patient with pseudo-polyps upon whom vagotomy has been performed. The patient did not like the idea of having an ileostomy, and vagotomy was second choice. Vagotomy was performed; she came back in four or five months with the thought in mind that we could now do a colectomy and low anastomosis. On proctoscopic examination the polyps had disappeared. For this reason she has had no further

surgery in spite of the reappearance of a single polyp in the last two or three months. We thought it better to follow this patient to see what happened.

I agree with Dr. Cave that where there are advanced changes that would suggest the occurrence of carcinoma, it would be unwise to do a vagotomy, thus letting more time go by for carcinoma to become fully established.

With regard to the length of time before fever and spasm disappear, there has been a good deal of variation. Most patients with fever had acute processes and, in most cases, the fever disappeared in three or four days. The disappearance of spasm was apparently very rapid, just as Dr. Dragstedt has pointed out in patients with duodenal ulcer.

Dr. Lahey mentioned the rapidity with which the process can develop. Two of our patients had very acute processes, and vagotomies were done in situations in which we felt that either conservatism or ileostomy would certainly result in the loss of the patient. Both have done very nicely. I agree with Dr. Holman that a much longer period of observation is necessary before any definite conclusion with regard to emotional responses can be formed.

PHARMACOLOGIC FACTORS INFLUENCING COLLATERAL RESPIRATION; POSSIBLE RELATION TO THE ETIOLOGY OF PULMONARY COMPLICATIONS* †

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In 1930 VAN ALLEN, LINDSKOG AND RICHTER[1] presented experimental and clinical evidence to show that the pulmonary segments of man and certain animals are not isolated units or end structures from the standpoint of their ventilatory function. These authors demonstrated experimentally, in vivo and vitro, that an obstructed segmental division of a lobe can obtain air from adjacent, freely ventilated segments. To this function of the obstructed pulmonary segment the term collateral respiration was given. (Fig. 1.)

Subsequently, the same investigators and their co-workers demonstrated that an obstructed segment may breathe through collateral respiratory channels at least 10% as much air as would normally flow through direct bronchial channels, and that the volume-flow of collateral air varies directly and proportionately, within certain limits, with the depth of respiration (tidal volume).[2] It was also shown that the volume-flow of collateral air is decreased by phrenicectomy and by tight abdominal binders, and that when unobstructed segments of a lobe are inflamed, swollen or consolidated from chemical or bacterial action, collateral respiration may be interfered with sufficiently to allow atelectasis to develop in the obstructed portions.[3]

By demonstrating the collateral passage of liquids and particulate matter it seemed certain that the major part of collateral respiration occurs through the pores of Kohn.[4] Convincing histologic evidence of the existence of these interalveolar communications in normal mammalian lungs was advanced by Ogawa[5] and more recently by Loosli.[6]

It is evident from these studies that collateral respiration has much the same economic role in the operation of the bronchial tree as collateral circulation has in that of the vascular system, for both act to conserve the function of the parts which have become obstructed. Collateral respiration minimizes the incidence of segmental atelectasis and renders assistance in bronchoelimination.[7] Because of the small pressure gradients involved, the mechanism is highly susceptible to interruption by many factors.

This physiologic collateral mechanism seems to fit well into the widely accepted obstructive theory for the etiology of postoperative pulmonary atelectasis, because the mechanical factors deemed most significant in its production,

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† Read before the American Surgical Association, May 28, 1948.

namely, pulmonary hypoventilation secondary to rigidity of abdominal muscles and wound pain, restraining dressings, pneumoperitoneum, and intestinal distention with resultant elevation of the diaphragm also interfere with collateral respiration.

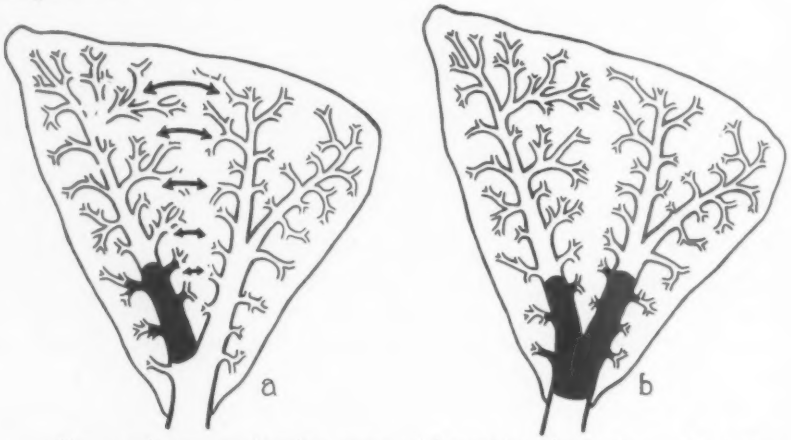

FIG. 1.—Diagram showing types of bronchial obstruction. (a) Lobular or segmental, which permits collateral respiration. (b) Lobar, which prevents collateral respiration.

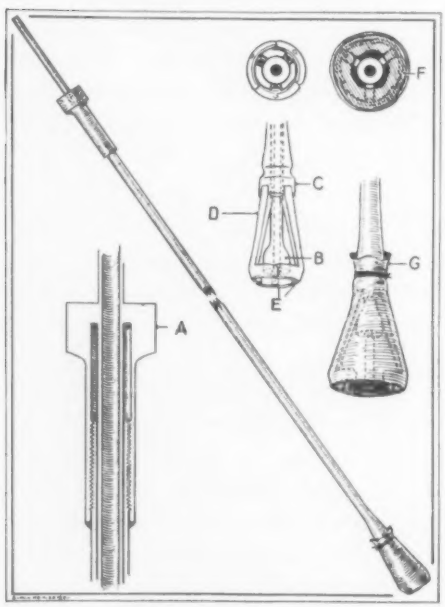

FIG. 2.—Diagrammatic sketch of dilatable bronchial cannuls. (Van Allen)

The clinical observation that these mechanical factors are not commonly operative in the extra-abdominal group of operations, a group in which a reduced but still substantial incidence of postoperative atelectasis is also seen, led Lindskog in 1941[8] to theorize that histamine-like substances are absorbed from sites of operative or other trauma which by their action of bronchial constriction and hypersecretion set the stage for the secondary action of already recognized and accepted mechanical factors. The latter determine the preponderantly higher incidence in the hernia-laparotomy group of operations.

That histamine-like products of cellular disintegration are absorbed systematically in tissue trauma has been demonstrated by Blalock[9] and by Katzenstein, Mylon and Winternitz.[10] During crush and tourniquet shock, respectively, these writers observed the appearance of a toxic substance in the thoracic duct lymph of dogs. The collected lymph when injected into normal

dogs elicited a histamine-like vasodepressor response in approximately one-half the animals.

To test this theory of a humoral factor in the development of postoperative pulmonary complications, inquiry was made into the effect of chemically pure histamine and certain antihistaminics on collateral respiration in dogs. This paper constitutes a report of the findings.

MATERIALS AND METHODS

For each experiment a healthy dog was anesthetized by intravenous injection of sodium pentothal, in dosages of 35 Mg. per Kg. body weight. A mid-

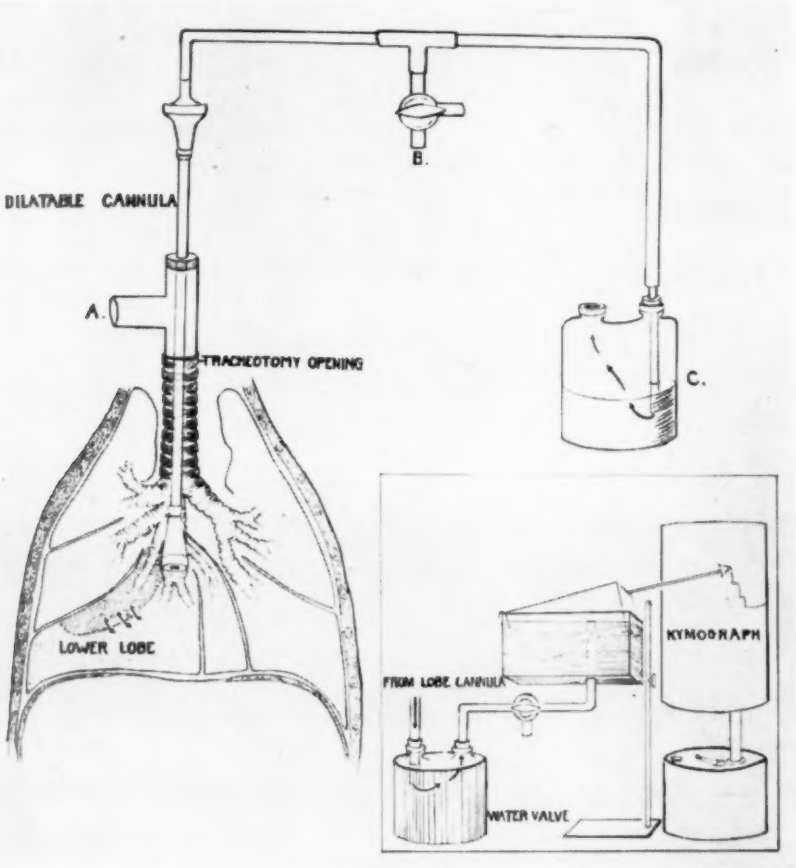

FIG. 3.—Detailed diagrammatic sketch of apparatus used for collection of air from obstructed lung segments. Insert: Arrangement for volume measurements of collaterally transpired air.

line cervical tracheotomy was then performed and a glass cannula was tied securely in the tracheotomy opening. The cannula was of approximately the same caliber as the trachea and had one side arm.

A long slender metal bronchial cannula with a dilatable tip[11] (Fig. 2) was introduced through the tracheal cannula to a point beyond the dorsal segment

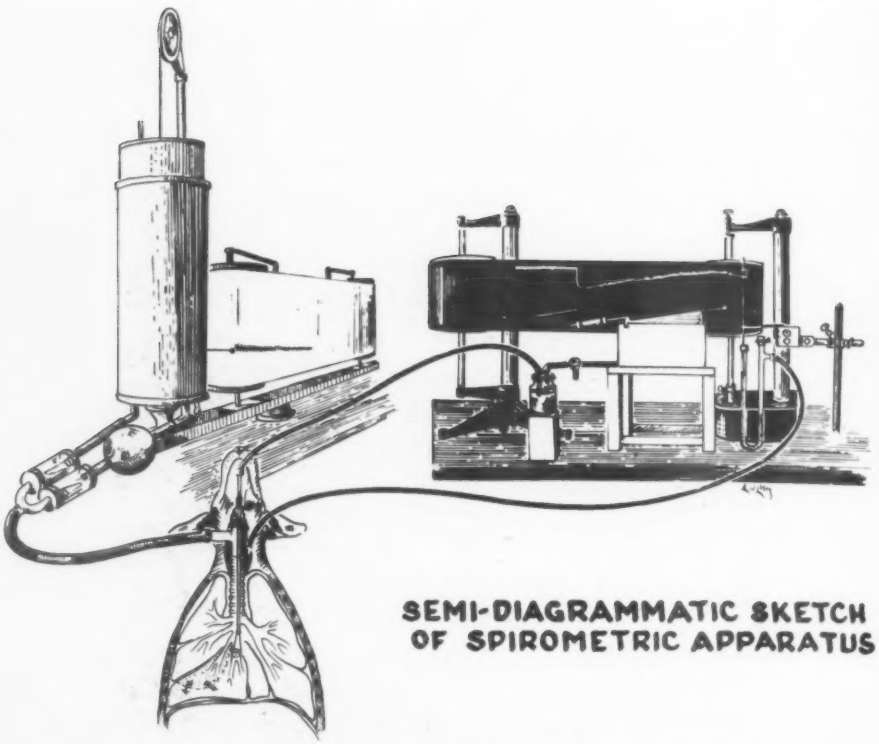

FIG. 4.—Semi-diagrammatic sketch of spirometric apparatus.

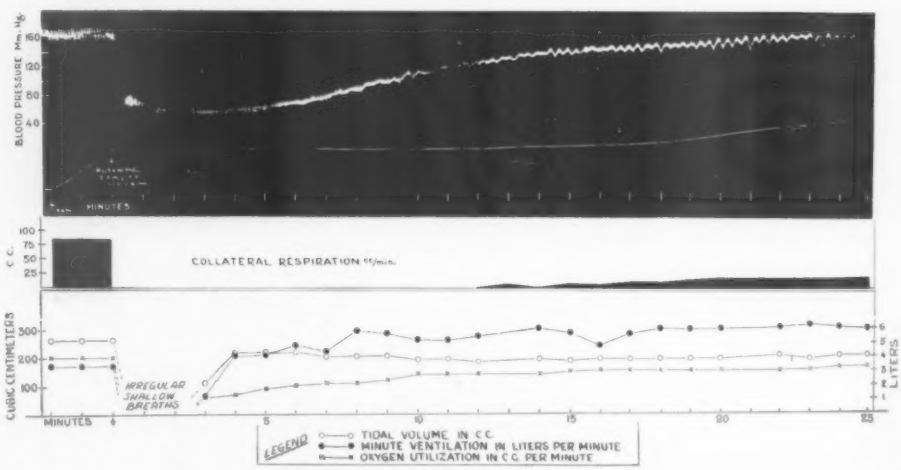

FIG. 5.—*Upper:* Photograph of actual kymograph record. Administration of 2.0 Mg. histamine causes hypotension, cessation of collateral respiration. Below the record is shown the calculated volume of collateral air in graph form.

Lower: Charted data obtained from large spirometer, showing transient decrease in tidal air and oxygen utilization, with tachypnoea reflected in increased minute ventilation.

bronchus of the right or left lower lobe. The tip was dilated firmly in place. The proximal end of the bronchial cannula was then connected to a delicately balanced and calibrated Krogh spirometer of 450 cc. capacity with a water valve interposed so as to permit expiration only. The rate of collection of the expired collateral air was recorded continuously from the Krogh spirometer on a revolving smoked drum. (Fig. 3.) The tracheal cannula opening through which the bronchial cannula passed was sealed with a rubber cuff and the side-

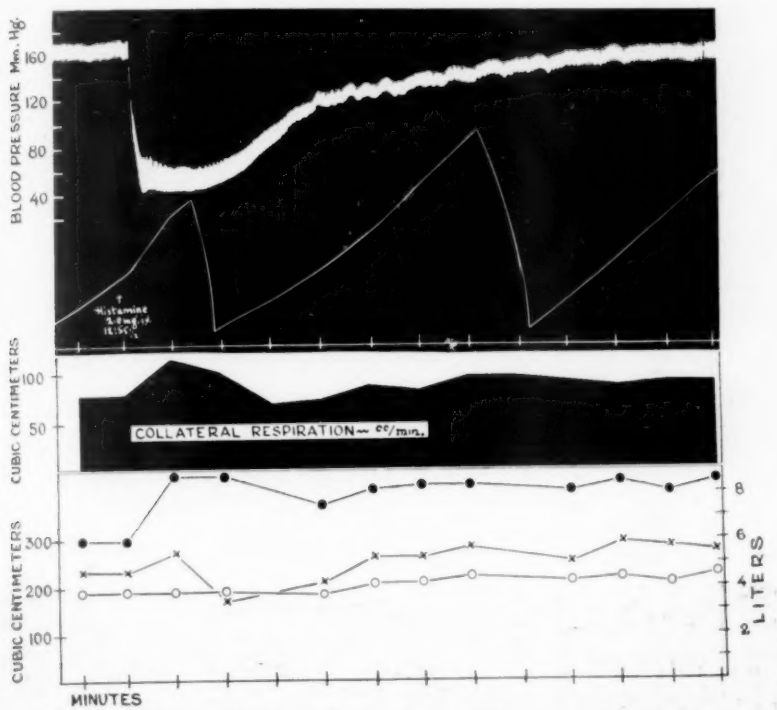

FIG. 6.—*Upper:* Photograph of kymographic record. Histamine 2.0 Mg. administered 13 minutes following injection of Benadryl 3.0 Mg. per Kg. No interference with collateral respiration, but some actual increase. Downward deflection of curve represents manual emptying of small spirometer.

arm was connected through a CO_2 absorber to a standard Roth-Benedict spirometer containing oxygen. This spirometer recorded on a second kymograph tracing the tidal volume, respiratory rate, and oxygen uptake for the unobstructed portions of the lungs. (Fig. 4.) Simultaneous carotid blood pressure tracing was also recorded.

After each experiment the dog was autopsied to check the position and tightness of the occluding cannula and to rule out the presence of gross pathology.

Six experiments were carried out in which histamine diphosphate was injected intravenously in varying dosages before and after the injection of Benadryl (b-dimethyl amino ethyl benzhydryl ether hydrochloride) and in one

experiment in which Pyribenzamine (N-pyridyl-N-benzy-N-dimethyl ethylene diamine monohydrochloride) was used instead of Benadryl. No effort was made to determine the relative potencies of these antihistaminic agents.

RESULTS

As in the human there was a wide range of individual sensitivity to histamine among these dogs. In all instances, however, histamine in doses of 0.02-2.0 Mg. resulted in a marked diminution or elimination of collateral respiration

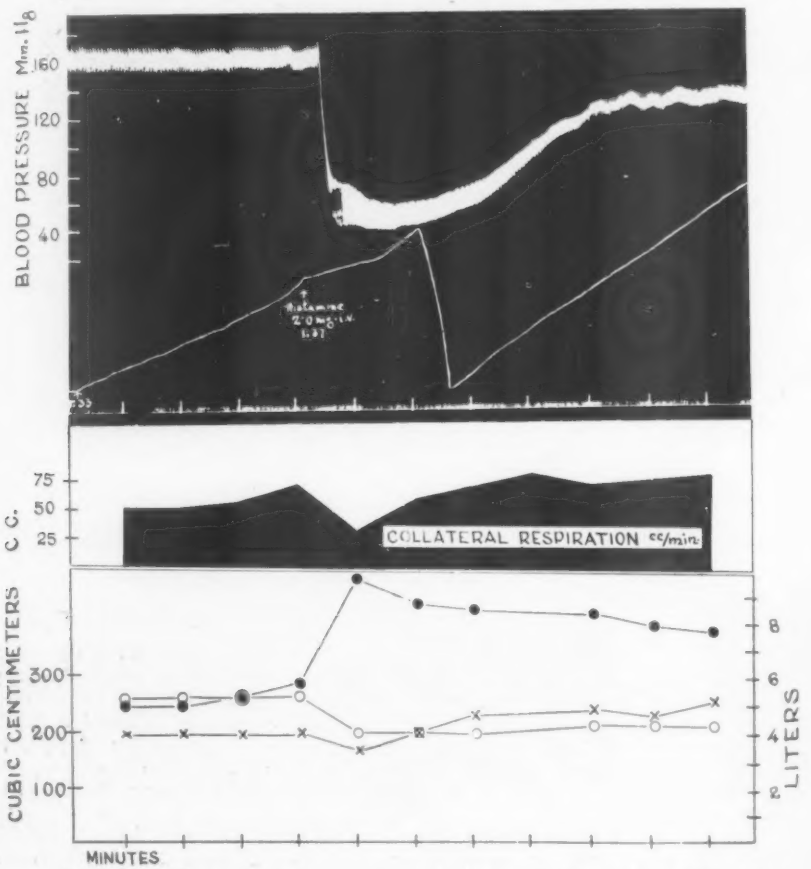

FIG. 7.—Effect of intravenous injection of histamine (2.0 Mg.) one hour following injection of Benadryl 3.0 Mg. per Kg. Note slight interference with collateral respiration.

followed by a gradual return of this function to the preinjection rate in a period of minutes. Associated with this phenomenon were marked tachypnoea, variable decrease in tidal volume, and a striking reduction in oxygen utilization for the whole animal. These were of shorter duration than the depression of collateral respiration. (Fig. 5.) The degree of response was found to be in proportion to the dose. Elimination of collateral respiration for a short period was observed in one animal with doses as small as 10 gamma per kilogram body weight.

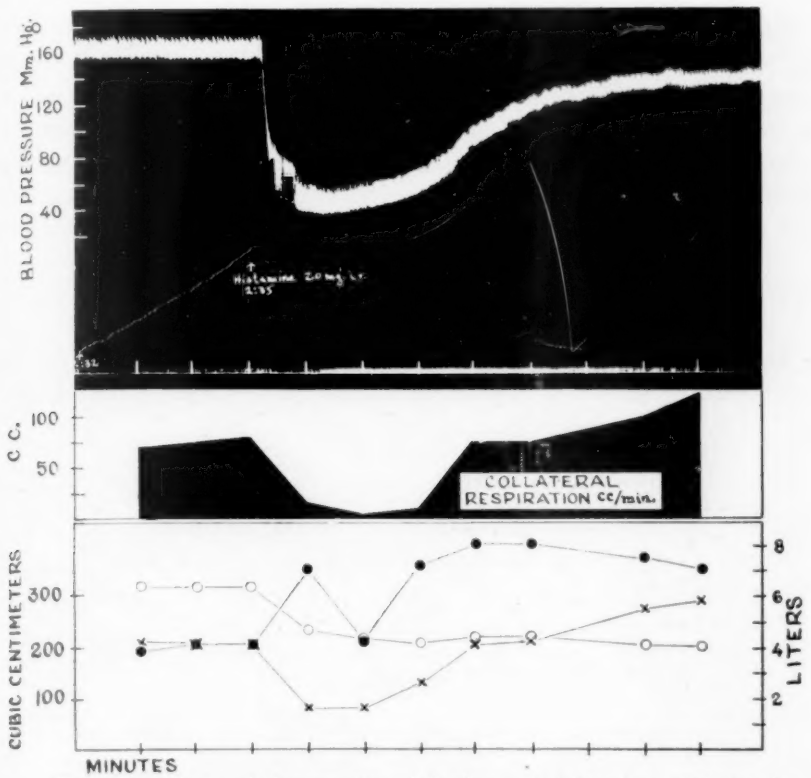

FIG. 8.—Effect of intravenous injection of histamine (2.0 Mg.) two hours following injection of Benadryl 3.0 Mg. per Kg. The protective effect of Benadryl is seen to be decreasing.

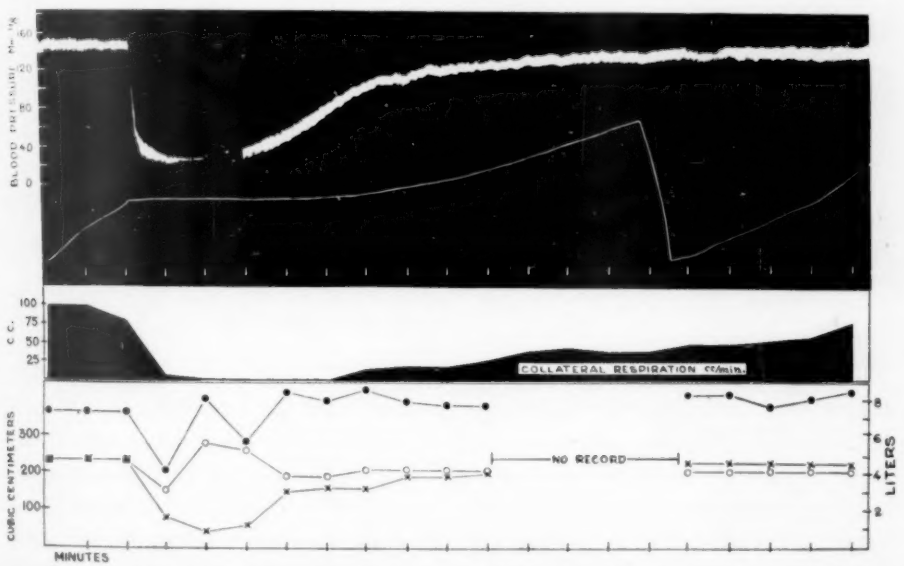

FIG. 9.—Effect of intravenous injection of histamine 2.0 Mg. five hours following the injection of Benadryl 3.0 Mg. per Kg. Further decrease in the protective effect of Benadryl is demonstrated.

Benadryl in doses of 1-3 Mg. per kilo and Pyribenzamine in a dosage of 1 Mg. per kilo given prior to injection of histamine completely eliminated the depressive effect of histamine on collateral respiration. In fact, the tachypnoea which resulted from histamine injection following Benadryl increased the rate of collateral respiration if the interval between injection was only a matter of a few minutes. (Fig. 6.) The protective effect of these agents was maximal for 1-1½ and 3 hours, respectively, and then disappeared gradually over the ensuing five or six hours. (Fig. 7-9). Benadryl was found to protect against single doses of histamine as high as 10 Mg.

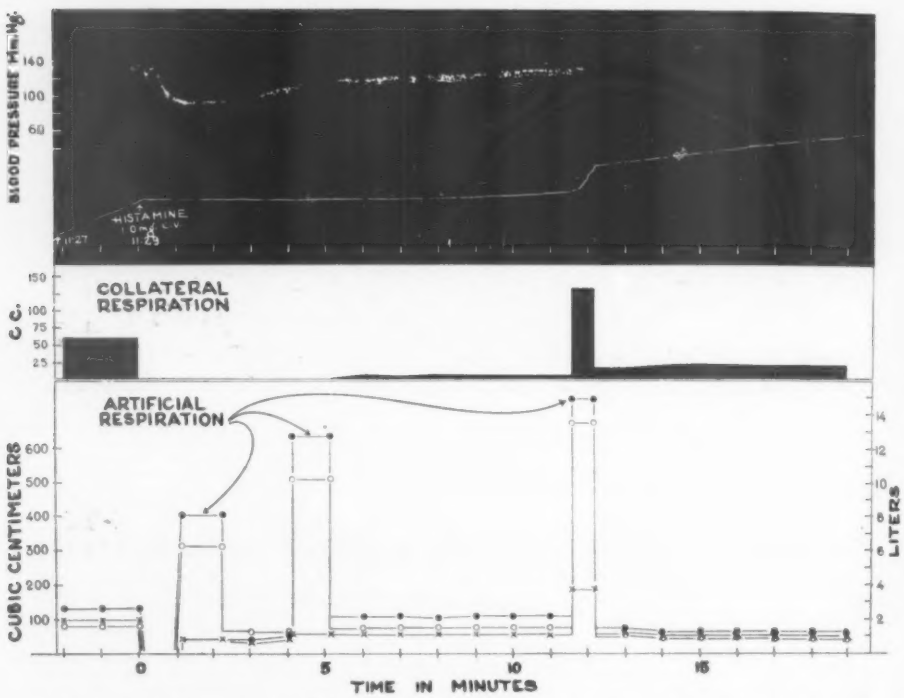

FIG. 10.—Vigorous artificial respiration performed by elevating and depressing the Roth-Benedict spirometer drum had no effect when collateral respiration was totally obstructed by histamine. Following the spontaneous return of this function artificial respiration increased the rate of collateral flow.

Note: The tidal volumes recorded during artificial respiration are exaggerated by the rise and fall of water in the spirometer jacket during this manipulation.

To rule out the decrease in tidal volume after histamine as an important factor in the reduction of collateral respiration other experiments were carried out. During the period when collateral respiration was blocked the animal was given forceful artificial respiration by manually elevating and depressing the large spirometer drum. No collateral respiration occurred. Following the spontaneous return of collateral respiration during the recovery period, however, artificial respiration resulted in a marked increase in collateral respiration (Fig. 10.)

Rapid intravenous administration of Benadryl in a dosage of 3 Mg. per kilogram caused a transient but marked fall in blood pressure, followed by a lesser and more prolonged hypertension.[12] Accompanying these vascular effects was a short period of apnoea followed by a decrease in tidal volume and increased respiratory rate lasting for several minutes. During the period of apnoea no collateral respiration occurred and there was a relative decrease in the rate of its production during the period of decreased tidal volume and increased respiratory rate. (Fig. 11.) These effects were not observed when the dose of Benadryl was injected slowly. The same effects, but of more marked degree, were observed following the rapid intravenous injection of Pyribenzamine, 1 Mg. per Kg.

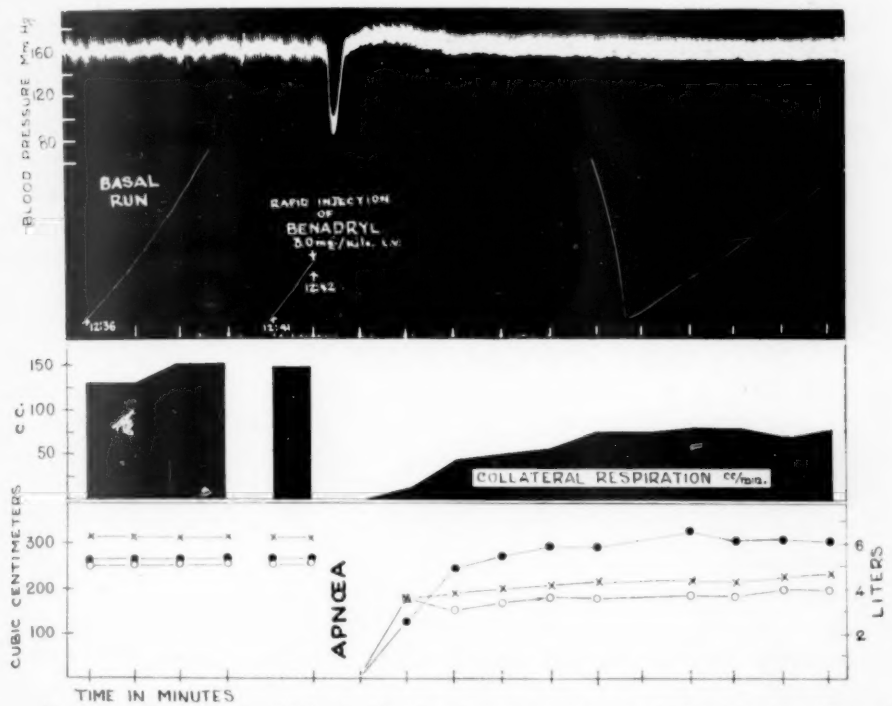

FIG. 11.—Showing the biphasic blood pressure response and decrease in collateral respiration in proportion to reduction in tidal volume following rapid intravenous injection of Benadryl 3.0 Mg. per Kg. No vascular or respiratory response was obtained following the slow intravenus infusion of the same dose.

DISCUSSION

The mechanism by which histamine interferes with collateral respiration is still conjectural. The bronchoconstrictor and edema-producing actions of this drug are well recognized. That bronchoconstriction alone is responsible seems unlikely in view of the fact that some oxygen uptake (although reduced) was present during the periods when collateral respiration was altogether absent. Studies with ANTU-induced pulmonary edema in dogs reveals that collateral respiration is eliminated before rales can be heard with the stethoscope.[13]

This suggests that pulmonary edema results in a thickening of the interalveolar membrane of sufficient degree to obliterate the pores of Kohn before sufficient fluid is exuded into the respiratory passages to be clinically evident as rales. That a degree of pulmonary edema may play a role in the collateral respiratory-blocking effect of histamine remains a possibility, but the rapidity of action makes this unlikely.

These observations also have an interesting relation to a side-action of curare, a drug which is now of widespread use as an adjunct in anesthesia. The intravenous injection of curare was shown by Anrep and his co-workers[14] to release histamine from muscle tissue in dogs, which circulated in the blood in physiologically active form. Subsequently, Comroe and Dripps[15] found that intracutaneous and intra-arterial injections of curare in man produced typical histamine-like wheals and flares. These observations were confirmed by Grob, Lilienthal and Harvey[16] who also described evidence of general vasodilatation and increased secretion of gastric juice following intra-arterial injection of curare, and found these to be inhibited by the previous or simultaneous injection of antihistaminic agents. Recently, Landmesser[17] measured the broncho-constrictor action of intravenous curare in dogs and found it to be inhibited by antihistaminics. The release of histamine following administration of curare may explain the reported occasional occurrence during curarization of alarming respiratory difficulty and sudden severe hypotension which resemble the effects of histamine.[18-22]

The effect of histamine on collateral respiration as demonstrated in this study suggests that histamine release by curare presents an additional factor in the production of postoperative pulmonary complications. However, this factor may be outweighed by the beneficial effects of curare, namely, shorter operating time and better exposure with less trauma. Thus far no report of a carefully controlled study of postoperative pulmonary complications following curare in anesthesia has been published.

If histamine-like substances are released by various types of tissue trauma, the facts established by our experiments suggest that the absorption of these substances following operative trauma may act to produce an interference with collateral respiration, thus setting the stage for the development of postoperative pulmonary atelectasis. Furthermore, this mechanism may be inhibited by prior administration of antihistaminics.

CONCLUSIONS

1. Histamine when administered to normal dogs in total dose of 0.02-2.0 Mg. causes a temporary abolition of the collateral respiratory function in the lung lobe.

2. This action of histamine is inhibited by prior administration of antihistaminics (Benadryl and Pyribenzamine).

3. The possible relation of these findings to the production of postoperative pulmonary atelectasis and its prevention is discussed.

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DISCUSSION.—DR. GUSTAF E. LINDSKOG, New Haven, Conn.: I think that the experiments themselves are reasonably clear cut. The link in the chain that is missing is evidence that in surgical operations and other types of trauma sufficint histamine is released and absorbed into the blood stream to cause this type of remote effect on the lung. Clinical experience suggests that there is a basic humoral mechanism in the production of early postoperative pulmonary complications. They occur

typically very early, and they occur preponderantly in patients who have had severe operative trauma and prolonged operations. There are two factors that the external or extralaparotomy group of operations and the internal or laparotomy group have in common. These are operative trauma and sedation, and sedation I think plays a very important role. However, the common primary mechanism may be the humoral mechanism, the effects of which we have tried to demonstrate here from the experimental side.

I would like to point out that with this cannulation technic, which was first developed by Dr. Van Allen in 1930, there exists an excellent opportunity for anesthetists to study very accurately and quantitatively the effect of certain agents on the peripheral pulmonary and bronchial mechanism.

DR. EDWARD D. CHURCHILL, Boston: Dr. Lindskog and his colleagues have taken up the problem of the point at which histamine or histamine-like substances act on smooth muscle in the lung. It has been known for years that the injection of a small amount of histamine is followed by a sharp rise in the pressure recorded in the pulmonary artery. The smooth muscle of the lung, however, is a very complicated structure. Its distribution varies widely in different mammals. In some species it appears most highly developed in the walls of the arteries; in others, in the bronchial tree. It is difficult to isolate and identify the action of these various components of the smooth muscle structure.

It occurred to us a good many years ago that the sharp rise of pulmonary artery pressure in response to a minute dose of histamine might be a method of biologically detecting the release of histamine from traumatized tissue. At that time the H-substance was in its heydey and everyone was attributing traumatic shock to H-substance. An experiment was set up, using the cat, with a constant recording of the pulmonary artery pressure. An extremity was isolated by a tourniquet and traumatized. The question asked was whether release of the tourniquet, which was found to cause a precipitate drop in systemic pressure, might also produce a rise of pulmonary artery pressure. The assumption was that a wave front of H-substance released from the traumatized extremity would enter the pulmonary circulation and produce a characteristic pharmacologic response. Actually, no detectible rise of pulmonary artery pressure occurred. When a minute dosage of histamine was placed in the venous system of the extremity before loosing the tourniquet, its release was followed by the characteristic effect.

Any conclusion regarding the release of H-substance from traumatized tissues should be clearly earmarked as an assumption. This hypothesis was set up by physiologists during and after World War I, on the basis of poorly controlled experiments and superficial clinical observations. It has taken years to put it in its place as an unproven assumption.

STUDIES ON THE USE OF POLYTHENE AS A FIBROUS TISSUE STIMULANT*

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ATTENTION WAS DIRECTED toward the irritating properties of cellophane by Page[2] in 1939, who wrapped the kidney of dogs in cellophone, in order to produce hypertension. Since that time, clinical and laboratory reports have been made showing successful obliteration of aneurysms and complete interruption of large blood vessels as a result of fibrosis secondary to cellophane implants. Concurrently, other reports have been made demonstrating the use of cellophane and cellophane-polythene (polyethylene) because of its physiologically inert characteristics and lack of fibrous tissue stimulating characteristics. In other words, clinical use is being made of an apparently similar or related substance with end results that are diametrically opposed.

Poppe and De Oliveira,[7] in 1946, reported the results of their studies of the comparative characteristics of various types of cellophane. They showed that substances identified as varieties of cellophane caused slight tissue reaction; whereas the substance referred to as polythene** caused a marked fibrous reaction.

Ingraham, in 1947, and in contradistinction to Poppe's findings, reported that polythene film and polythene tubes were implanted into the brains of experimental animals without evidence of gross or histologic tissue reaction. In contrast to the work of Poppe and De Oliveira, he also demonstrated marked tissue reaction to du Pont "Cellophane (PT 300)", a substance which Poppe had found to be comparatively inert.

Personal correspondence with the du Pont Company has elicited the comment that there is apparently some confusion in identity between cellophane and polythene, and that in their experience, this had not been unusual even in commercial application.

Implantation, into human tissue, of foreign substances other than suture material, has been attempted to correct or reinforce tissue defects or to bridge over breaks in tissue continuity. Bone plates, vitallium tubes and lucite balls all represent recent examples of this principle. Such substances are useful because of their physiological inertness and because they produce minimal tissue reaction. Certain varieties of cellophane apparently meet this requisite. Donati,[1] in 1936, demonstrated the inert characteristics of cellophane. Wheeldon,[3] in 1939, reported the use of No. 300 moisture proof transparent cellophane, as a permanent tendon sheath, to prevent adhesions. In 1943, McKeever[6] reported the use of cellophane following synovectomy, as an interposition membrane, to prevent adhesions of two surfaces.

* Read before the American Surgical Association, Quebec, Canada, May 28, 1948

** Polythene; cellophane-polythene and polyethylene are synonymous terms.

In September, 1947 at the Clinical Congress of the American College of Surgeons, reports were made by Brown, Gunlay and Craig: "Use of Polythene As A Dural Substitute"; by Gunlay and Gray: "Molded Plastic Tubes: An Experimental Study With Special References To Their Use In Reconstruction Of The Common Duct", and by Hockworth: "Replacement Of The Thoracic Aorta With Polythylene Tubing: An Experimental Study".

Our interest in the problem has evolved from a search for a substance that will cause a relatively controlled fibrous tissue stimulation, without, at the same time, having the undesirable characteristics of a foreign body. Laboratory and clinical studies have confirmed our impression that "polythene-du Pont" meets these requirements. We prefer the latter terminology in order to clarify the present misunderstanding regarding the characteristics of various types of cellophane and polythene. Disparities noted in results with polythene are apparently not due to variations of the basic chemical formula or the raw product, but upon the method by which it is secondarily converted into film, blocks or tubes. For purposes of clarity, discussion in this paper will be limited to the effects of "polythene-du Pont" as obtained in 1.5 mil film directly from the E. I. du Pont De Nemours and Company Inc. This company prepares polythene film from crude polythene by a "solvent cast" method. The finished product is pure polythene with the exception of less than one percent of dicetyl phosphate, the stripping agent.

Other manufacturers prepare polythene film and polythene tubes, from crude polythene, by means of a "melt extrusion process". This process does not entail the use of antioxidants, stripping agents or plasticizers, the end product being pure polythene.

In attempting to correlate the results of various investigators, this variation in method of manufacturing was noted. The implications, which are obvious, will be discussed under animal experimental implant data.

Inertness and minimal tissue response associated with implantation of foreign substances are essential characteristics, when indicated. Nevertheless, in certain conditions, there is need for a substance for tissue implantation that will stimulate, within reasonable limits, the production of fibrous tissue.

The desirability of occluding aneurysms has been understood since their recognition as a clinical entity. Ideally, the procedure should occlude, or in some way eliminate the aneurysm without jeopardizing the distal circulation. The concept of gradual arterial obliteration was originated late in the 18th century. Various ingenious externally compressing devices were ultimately found to be unsatisfactory, and not without their dangers. Direct attack is frequently limited, both by reason of endangering viability of tissue and by anatomical difficulties. A procedure that will gradually obliterate an aneurysm with absolute certainty, and not entail the use of mechanical devices, or repeated operative procedures, should assure an optimum distal circulation.

Polythene-du Pont falls into the category of a plastic, it being a long-chained polymer of ethylene. As stated previously, this product is pure poly-

thene with the exception of less than one percent of dicetyl phosphate. In medical literature, polythene is usually referred to as polyethylene. When it was found that polythene-du Pont possessed fibrous tissue stimulating qualities, possible carcinogenic excitant characteristics were excluded. The latter observations extended over a period of five months. Polythene-du Pont implants were made into 20 mice, representing two cancer susceptible strains and two cancer resistant strains. Co-carcinogenic agents (Hematoporphyrin and Croton oil) were also injected. The implantation of polythene-du Pont into mice did not give rise to tumors, or reveal evidence of carcinogenic stimulus.

Fibrous tissue stimulating characteristics of polythene-du Pont were studied in a series of animal experiments that included dogs, rabbits and guinea pigs. Following its implantation, microscopic and histologic studies were made at intervals of 10 days, and one, two and three months. Paralleling control studies were also made. It was found that polythene-du Pont caused an inflammatory response in tissue, far in excess of that seen in control animals. This inflammatory reaction was characterized by edema, hyperemia, fibroblastic proliferation and lymphocytic and eosinophilic infiltration. Effects on fascia, muscle and peritoneum, as well as blood vessels, were studied. (Fig. 1 & 2.) Implants were sutured in situ, and their location carefully marked.

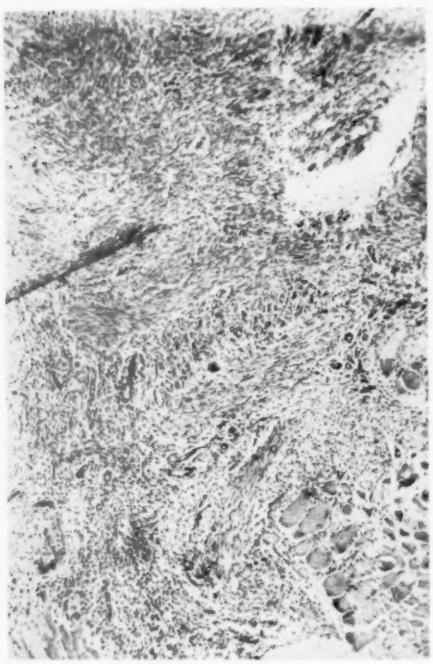

FIG. 1 (Guinea Pig 10).—Low power photomicrograph of the implantation site of polythene-du Pont, thirty-four days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Note the extensive fibrosis. Areas of scarring are composed of fibroblasts, in a loose stroma with young fibrocytes arranged in whorls. Histocytes laden with blood pigment are present.

In addition to these observations, crude polythene flake, polythene film prepared by the "melt extrusion" process, which is pure polythene, as well as dicetyl phosphate were implanted into the tissues of experimental animals. The results of these observations are shown in Fig. 3, 4 and 5.

Based on these observations, we believe that pure polythene is comparatively inert when implanted into tissue, and does not cause a fibrous tissue reaction. Polythene film prepared by the "stripping process" of the du Pont Company is adulterated by dicetyl phosphate. Apparently the tissue excitant

factor noted in polythene-du Pont is dicetyl phosphate with polythene simply acting as an inert media of transmission.

The effects of polythene-du Pont on a diffuse dilatation of the common carotid artery and on a fusiform aneurysm of the abdominal aorta are illustrative of the clinical application of the principle of treatment by fibrosis.

CASE REPORTS

Case 1.—M. E. W. (History 35073), a 66-year-old white female admitted to the University Hospital with a complaint of "hoarseness" associated with a "lump" in the right side of the neck. Three years previous to admission, she noticed difficulty in singing, and an increasing hoarseness. There were no complaints of cough, palpitation, dyspnea or syncope.

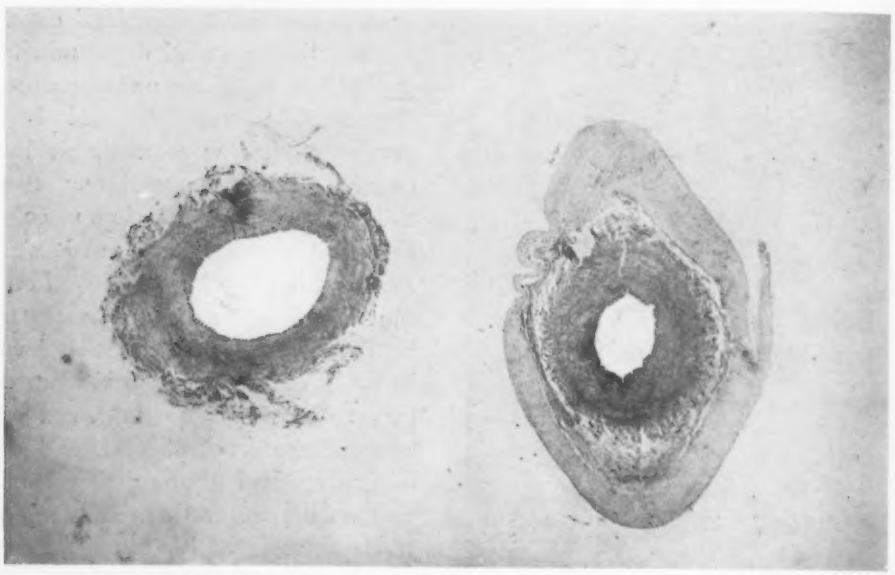

FIG. 2 (Dog 11).—Low power photomicrograph. A—Normal carotid artery. B—Carotid artery thirty-eight days after implantation of polythene-du Pont. Note the substantial constriction. The adventitia and periadventitia is thickened with dense collagenous connective tissue. Focal lymphocytic infiltration is present. The media is free of significant scarring.

A pulsating mass, synchronous with the heart beat, just above the right sternoclavicular area was noted. It measured approximately 5 cm by 3 cm. No thrill or bruit were present. The radial pulses were equal and synchronous; the heart slightly enlarged, to the left. Serology negative. Roentgen examination:—Moderate cardiac hypertrophy; aorta tortuous but not dilated; no soft tissue mass seen in the lower cervical region.

Under endotracheal cyclopropane anesthesia, the right cervical area was explored. The right subclavian artery was sclerotic and tortuous. The right common carotid artery was tortuous and markedly dilated, simulating a fusiform aneurysm. The innominate artery was also sclerotic and dilated. The common carotid was mobilized and the internal juglar vein and vagus nerve, as well as the recurrent laryngeal nerve, were isolated. A single layer of 1.5 mil polythene-du Pont was overlaid about the common carotid artery, and tacked in place with interrupted double zero plain catgut sutures. The bifurcation of the innominate was overlaid in a similar manner. The incision was closed without drainage.

The postoperative course was essentially without event. The patient returned to work at the end of four weeks, after operation. Examination at the end of four months, revealed no evidence of hoarseness, and no history of recurrence of hoarseness. The mass in the right side of the neck had disappeared. Pulsations in the right carotid region, were within normal limits.

Case 2.—G. F. (History 36376), (Fig. 6), a 64-year-old white male, admitted to the University Hospital with a complaint of a "throbbing lump" in the left lower abdomen, and weakness of the left lower extremity with cramping. The "weakness and cramping" were noticed about one year prior to admission to the hospital. Following development of the leg symptoms, a hard mass was noted in the left side of the abdomen, that gradually increased in size.

FIG. 3 (Rabbit 4).—Low power photomicrograph of implantation site of crude polythene flake 15 days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Defects that are seen represent polythene deposits. Infiltration of lymphocytes and polymorphonuclears is characteristic of a foreign body reaction.

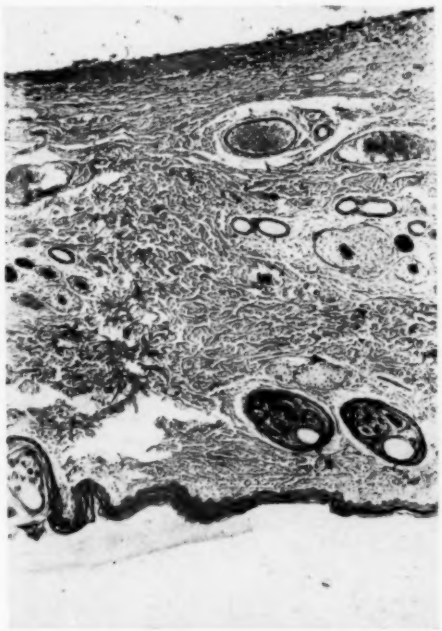

FIG. 4 (Dog 22).—Low power photomicrograph of implantation site of pure polythene film ("melt extrusion process") 12 days after its introduction into the subcutaneous plane of the abdominal wall (hematoxylin and eosin). Note the narrow margin of scarring and tissue reaction along the site of polythene implant. Giant cell and lymphocytic infiltration is minimal.

Physical examination:—Evidence of generalized arteriosclerosis, with an expansile, pulsating mass about 3½" by 4", to the left of the abdominal midline, nonadherent to the abdominal wall. Blood pressure in the right leg was 130/70; it could not be obtained on the left. Peripheral vessels, including the femoral, could not be palpated on the left side; all vessels were easily palpated on the right. The left foot was cool and ischaemic. Pulsations in the abdominal mass were synchronous with the heart beat. Neurological and Serology examinations were negative. E. K. G.:—Myocardial abnormality and possible coronary disease. Roentgen examination:—Aortic arch calcified; extensive calcification of the abdominal aorta with marked enlargement, the left

lateral border extending about 5 cm. lateral to the lumbar vertebra; calcification noted from L 2 to the lumbosacral joint. Definite bony erosion not seen. The colon, by means of barium enema, filled readily with no filling defects and no displacement.

Under spinal pontocain anesthesia, an abdominal exploration was performed through a long left muscle splitting incision. A fusiform aneurysm of the abdominal aorta was found that extended from the level of the first lumbar vertebra, to its bifurcation into the common iliacs. The jejunum, at its point of fixation by the ligament of Treitz, was displaced forward, and was adherent to the aneurysm. The peritoneum was reflected from the aneurysm, and the aneurysmal sac exposed over about 80 percent of its surface. The right common iliac appeared to be normal in character. The left common iliac was distorted and compressed by an overlying bulge in the aneurysmal sac; very feeble pulsations were obtained in this vessel. The vena cava was visualized. No attempt was made to mobilize the posterior aspect of the aneurysm, overlying the vertebra.

FIG. 5 (Rabbit 3).—Low power photomicrograph of implantation site of dicetyl phosphate 13 days after its introduction into the muscles of the abdominal wall (hematoxylin and eosin). Note the fibrosis and lymphocytic infiltration. Foreign body giant cells are scattered throughout the section. with young fibrocytes arranged in whorls.

Single strips of 1.5 mil polythene-du Pont were tacked over the exposed areas of the aneurysm by means of fine silk sutures. Cellophane was overlaid along the medial margins of the exposed aneurysmal sac, in order to afford protection to the vena cava. The reflected peritoneum was then approximated by means of interrupted silk sutures. The abdominal incision was closed without drainage.

The postoperative course was essentially without event. Examination two months postoperatively revealed that the patient had returned to his occupation as a watchman. The abdominal mass, by palpitation, had decreased in size about two-thirds. The subjective sensation of "throbbing" had disappeared. He was completely free of pain. Particularly noteworthy, was the fact that pulsations were obtained in all of the peripheral arteries of the left lower extremity, as well as the right, and that both feet were warm.

IMPLANTATION OF POLYTHENE-DU PONT INTO THE ABDOMINAL WALL

The end effects of polythene-du Pont are apparently due to fibrosis. It was noted that experimental animals with large fascial and muscle defects fibrosed without evidence of herniation following polythene-du Pont implants, whereas these defects persisted in control animals. (Fig. 7.)

In general, foreign substances retard rather than aid the normal process of wound repair. Jenkins,[10] in 1947, in his studies with gelfoam sponges, stated "fibroplasia develops rapidly under the sponge, and in addition, invades the interstices of the sponge. This offers a lattice work for the growth

of fibroblasts, thus giving reinforcement and structural support".

More recently, Koontz[11] has studied the effects of tantalum mesh in the repair of ventral hernias. He has shown that when tantalum mesh is implanted into tissue defects, the mesh becomes covered by a very thick, tough envelope of fibrous tissue.

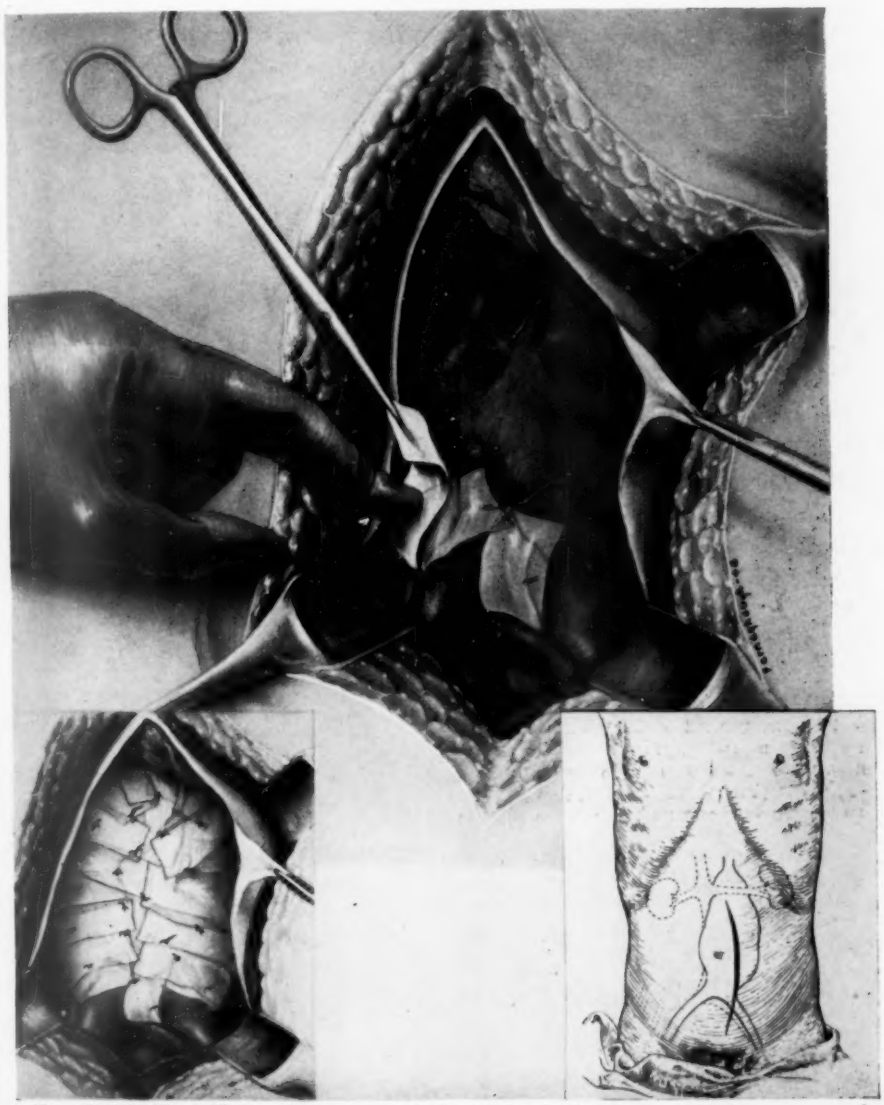

FIG. 6 (G. F. 36376).—Aneurysm of the abdominal aorta, secondary in arteriosclerosis, extending from L 1 to its bifurcation into the common iliacs. Peritoneum reflected from aneurysmal sac, and polythene-du Pont being plicated onto its wall.

Experimental studies were not made to determine the possible merits or advantages of these substances. It was thought that the type of fibrous tissue reaction noted with polythene-du Pont might be both desirable and advan-

tageous in the problem of recurring hernias, particularly in those associated with large fascial defects. This principle has been applied clinically in 15 instances, the following of which is a typical example.

CASE REPORT

Case 1.—J. M. G. (History 36335), (Fig 8) a 50-year-old white male, admitted to the University Hospital with a complaint of bilateral recurrent inguinal hernia. Bilateral inguinal hernioplasties had been performed 15 years and 3 years respectively, prior to the present admission. During a six to seven months period previous to this admission, it had been noticed that the hernia on the right side "bulged into the scrotum."

A B

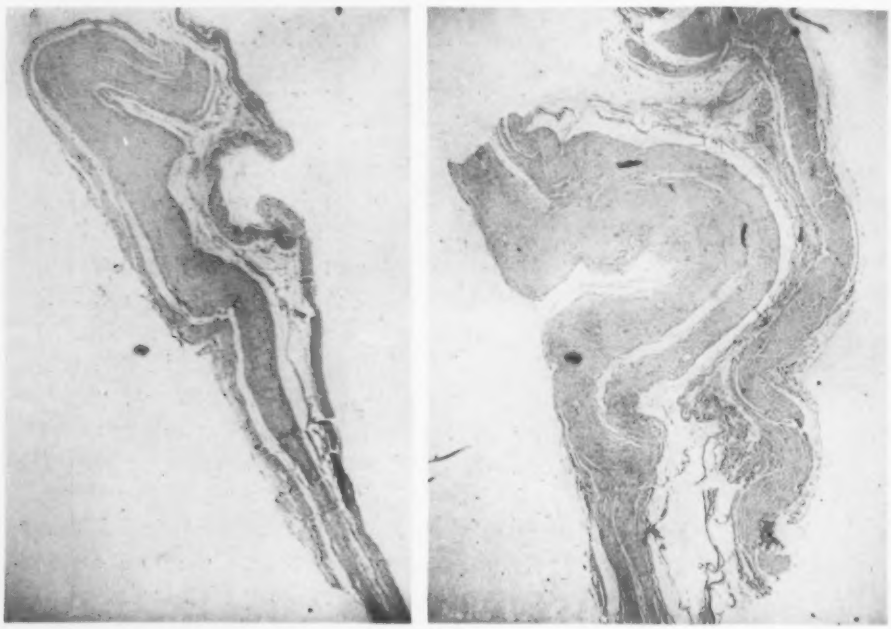

FIG. 7 ("a"—Dog 19; "b"—Dog 20). Low power photomicrographs showing "a"—control cross section of anterior abdominal wall 54 days after rectus muscle and anterior rectus sheath had been removed. "b"—same procedure 54 days after implantation of 1.5 mil polythene-du Pont into defect. Note greater fibroblastic proliferation and scarring in "b" as compared to "a".

Physical examination was essentially negative except for a complete irreducible inguinal heria on the right, and an incomplete reducible inguinal hernia on the left.

Under spinal pontocain anesthesia, bilateral inguinal hernioplasties of the Halstead type were performed. The right side entailed considerable difficulty in identifying anatomical planes. The sac on this side, which was densely adherent, extended into the scrotum, and contained incarcerated omentum, which was resected. Following ligation of the peritoneal sacs on their respective sides, a single strip of 1.5 mil polythene-du Pont was tacked over the neck of each sac. Another strip was placed between the peritoneum and the site of approximation of the conjoined tendon, to Poupart's ligament. This strip extended from slightly above the internal ring to the pubis. An additional strip of 1.5 mil polythene-du Pont was placed anterior to these approxi-

mated structures, and beneath the fascia of the external oblique muscle. The incision was then closed without drainage. The conjoined tendon in this patient was thin and transparent. The fascia of the external oblique muscle was a poorly defined structure. Except for a superficial infection, the patient's convalescence was comparatively without event. At the end of ten days, the incisional areas were brawny and indurated. This brawniness and induration persisted for about six weeks. Follow-up examination at the end of five months, did not reveal any suggestion of recurrence.

COMMENT

Polythene-du Pont implants have now been used in eleven inguinal hernias and in four of the ventral type. In each instance, the problem either

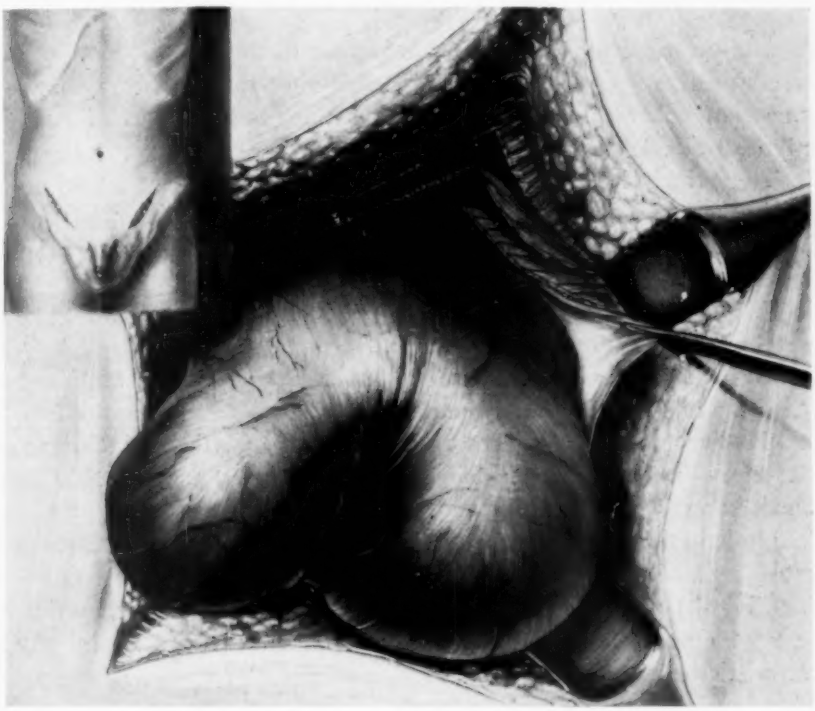

FIG. 8 (J. M. G. 36335).—Third recurrence, bilateral inguinal hernias, showing size of sac on right side which contained incarcerated omentum.

of repeated recurrences, or large fascial defects was presented. With the exception of the case reported above, none of the operative procedures were associated with secondary infection or unusual complications. The series is too small, and the period of postoperative observation too short, to establish a true evaluation of the effectiveness of this procedure. There has been no evidence of recurrences. The longest postoperative period of observance in this series is eight months; the shortest three months.

DISCUSSION

Polythene-du Pont, because of its fibrous tissue excitant characteristics, was utilized in the treatment of aneurysms and recurrent hernias. In retro-

spect, it appears that the same result could have been accomplished by the direct use of dicetyl phosphate, the chemical adulterant appearing in this type of polythene. Dicetyl phosphate, when implanted into the tissues of experimental animals, causes a prompt and violent type of fibrous tissue response. A supplemental report will attempt to demonstrate its late effects on tissue, as well as principles involving its utilization.

Some absorbable substance may ultimately prove to be a more satisfactory medium for application. If dicetyl phosphate can be combined with a substance such as gelfoam, the results should be more advantageous.

CONCLUSION

1. The principle of tissue fibrosis offers a method of obliterating aneurysms. It presents the advantages of gradual obliteration, with optimum development of collateral circulation. It has the disadvantages of not being directly controllable.

2. The principle of fibrous tissue stimulation may offer a field of usefulness in the problem of fascial defects and recurring hernias.

3. Polythene-du Pont represents a method of accomplishing a relatively controlled type of fibrous tissue reaction.

4. The type of reaction noted with polythene-du Pont seems to be due to dicetyl phosphate and not to polythene.

5. Pure polythene implants are well tolerated by tissues and are associated with a minimal tissue response.

6. Conflicting results regarding the use of polythene in aneurysms, patent ductus arteriosus, and obliterative procedures are probably due to variances in method of manufacturing the film.

7. Implantation of polythene-du Pont when fibrous tissue reaction is not indicated would be most undesirable.

8. Clinical use of cellophane, polythene or any other plastic, carries with it the urgent requirement of knowledge of both the chemical and physical characteristics of the product being used.

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DISCUSSION.—DR. HILGER P. JENKINS, Chicago: Dr. Yeager has drawn to our attention that a manufacturer uses an irritating substance such as diacetyl phosphate in the fabrication of the finished product, which makes a very striking difference in the behavior of this material in the tissues. This brings up the question of asking the Council on Pharmacy and Chemistry of the American Medical Association to co-operate with the surgical profession by maintaining a comprehensive file on new commercial materials which may be of value in surgery, so that those who are pioneering with these new products may have the benefit of information which may not be made available to individuals by manufacturers, unless one is as persistant as Dr. Yeager has been.

DR. HERMAN E. PEARSE, Rochester, N. Y.: I know of no subject on which there is so much confusion as in the physiologic response to plastics. There are four papers that can be used as an illustration. Poppe and Yeager have pointed out the irritant properties of polythene; Ingraham and Clagett have used polythene to prevent irritation.

Some years ago I reported on the occlusion of great vessels by wrapping them with cellophane. Later I carried out another group of experiments and could not repeat my original results. Experiments were undertaken to determine why this occurred. They were predicated on three hypotheses: One, that there was an individual sensitivity of the animal, and this has not been proven or disproven. Second, that the cellophane itself was impure and some contaminant in it caused the irritation. That has been demonstrated here, and I certainly congratulate Dr. Yeager. However, I do not believe that this can be the only irritating substance, for many possible contaminants are used in the manufacture. The third possibility is that the cellophane itself may be irritating and there is a coating on it that protects it from the tissue. This thought was suggested by the fact that if you soak it for a long time, or if you use various methods of sterilization, your results will differ. The greatest activity is obtained when the substance is boiled.

We have compared 300 P T cellophane from Dupont, 300 P U T from Dupont, polythene from Dupont, polythene from the manufacturer who supplied Ingraham, a number of cellulose products providede me, and to date the more I work in this field the more confused I become. The results are erratic.

I wish to conclude with one thought. If one uses these substances to produce irritation and they do not do so, you have not obtained your objective but you have done no harm. Should one use them to avoid irritation and have them cause irritation, I agree with Dr. Yeager, that the results will be catastrophic.

DR. DANIEL C. ELKIN, Emory University, Ga.: We have employed polythene in conjunction with a partial occlusion of the arota by a metallic band, in order to bring about a subsequent complete occlusion as a result of the fibroblastic cellular response to this material. The early experience, particularly that of Halsted, showed that the use of a metallic band alone frequently resulted in ischemia of the vessel wall

with subsequent rupture. The use of polythene or of some other irritating variety of cellophane, as advocated by Pearse, at times brought about a complete obliteration of the vessel but failed to produce uniformly a complete occlusion. We, therefore, combined the two methods, using a cuff of polythene about the aorta of the experimental animal, and over this placing a metallic band of tantalum so compressed as to produce about 50 per cent occlusion. It is believed that the fibrosis produced by the polythene serves to protect the vessel from erosion of its wall by the metallic band. Microscopically, it is readily seen that a heavy buffer of fibrous tissue is produced at the margin of the band and extends along the course of the artery as a bulkhead against erosion and aneurysmal formation. The vessel beneath the band continues to atrophy, but the entire area is encased in a sheath of fibrous tissue. Thus, the use of the two materials overcome the inherent disadvantages of either material alone, and the period of time required for complete occlusion of the artery is greatly decreased.

Dr. Amos R. Koontz, Baltimore: Dr. Yeager has certainly put his finger on one thing that is much needed in surgery; that is, something to increase fibrous tissue in various places. There is one place in which I have been trying to find something that will increase fibrous tissue; namely, in reinforcing suture lines, especially in hernia repair. I have tried various agents experimentally, such as gelfoam and fibrin foam, without very startling results, hoping to find something to cut down the use of some of those noxious agents our President spoke about yesterday.

The reports I have seen in the literature by Ingraham and others who have used polythene to repair dural defects state that it is inert, causes no irritation and no increase in fibrous tissue. The irritating type of polythene, which Dr. Yeager has used and which causes an increase in fibrous tissue, should be of great value in reinforcing suture lines when weak structures are sutured together. In a great many cases, especially in hernia repair, there are no available tissues surrounding the defect with which to strengthen the suture line. The possibilities of the irritating type of polythen in these cases are well worth considering.

I am going to have the temerity to speak of one of the agents that Dr. Gallie condemned yesterday; that is, tantalum mesh. I have tried this experimentally in dogs, resecting the rectus muscles on each side and replacing them with tantalum mesh sutured to the fascia around the edges of the defect, and leaving nothing but the tantalum mesh between the subcutaneous tissue and the peritoneum. It is remarkable to note, several months later, the amount of fibrous reaction that develops. The fibrous tissues grow through the mesh, all around the mesh, and it becomes covered with a very heavy layer of fibrous tissue and gives a strikingly firm abdominal wall. Whether the tantalum mesh stimulates fibrous tissue to grow, I do not know; but I have in mind some experiments to try to find out whether this is the case or whether the tantalum simply acts as an inert framework to support the growths of fibrous tissue. I have used it in a good many cases of large ventral hernia, in which the defect couldn't be closed and where there were no tissus to be mobilized to close the defect; or, if tissues were available, they were too weak to be of value. Of course, you can undercut, you can make flaps, you can make relaxation incisions; but even then the tissues are very weak in many cases, and if you haven't something strong to close the defect with, you will not get a cure.

I operated on one woman, using tantalum mesh, who measured 60 inches in her stocking feet and weighed 256 pounds in her nightgown, and the fat was actually oozing through all her fascial tissues everywhere. I do not think she could be cured without putting in some extraneous material. Maybe polythene will do the trick in these cases. When I saw Dr. Yeager's paper on the program, I already had some polythene to try out; and I am going to try it because if it will do the same thing for ventral hernias that tantalum mesh will do, it is possible it might be more desirable.

PROTHROMBIN ACTIVITY*

A Diagnostic Test for Early Postoperative Venous Thrombosis

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THE PREVENTION OF POSTOPERATIVE VENOUS thrombosis and pulmonary embolism has received a great deal of attention during the past few years. Sufficient clinical data have been accumulated to establish definitely that modern prophylactic methods can materially reduce the incidence of post-operative thrombo-embolism. This decreased incidence is due primarily to the use of proximal vein ligation and/or anticoagulants, but recent improvements in pre- and postoperative care have also played a definite role. Allen and associates [1] have been the foremost advocates of vein interruption. Heparin has been used most extensively in Sweden [2] and dicumarol has been favored in this country by Barker [3] and others. Each of these methods, or combination of methods, has its firm advocates but experience has shown that any one of the three can be effective when properly used. (Table I)

These methods present serious problems. Routine prophylactic bilateral vein ligation entails an added operating room procedure. Many surgeons view with alarm large scale normal vein ligation, and there is reason to believe that edema of the legs and other complications occur in some individuals as a result. Routine prophylactic postoperative anticoagulants require very careful laboratory control if they are to be both safe and effective. This is especially true with dicumarol, as the dosage must be individualized for each patient and plasma prothrombin activity must be determined daily during the treatment. This is a major technical and economic problem for the well equipped hospital and an insurmountable problem in the hospital with inadequate laboratory facilities. If the problem of thrombosis is approached statistically, only about 6% of postoperative patients require prophylaxis, but there has been no proven method by which this relatively small group can be distinguished from those patients who will not have thrombosis. Our recent experience indicates that the prothrombin activity of the plasma in the postoperative period may serve as a helpful test in predicting those patients who are liable to thrombo-embolic complications.

Our first efforts to find a laboratory test which might be of value in detecting early thrombosis were stimulated by the work of Waugh and Ruddick.[4] They used a heparin dilution method of determining blood coagulation time and found the time was decreased during bed rest, in

* Read before the American Surgical Association, Quebec, Canada, May 28, 1948.

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acute inflammatory conditions, in the presence of hemorrhage, and during the postoperative period. Using this method we have found marked reduction in coagulation time in several postoperative patients who developed thrombosis. Increased whole plasma prothrombin activity was also noted in those patients who developed thrombosis. The determination of the prothrombin activity of plasma is a simple laboratory procedure, and it seemed worthwhile to study its alterations in the postoperative patient.

There are conflicting reports in the literature concerning the relation of prothrombin activity to thrombosis. Tuft and Rosenfield[5] concluded from their studies using dilute plasma that an acceleration of prothrombin time is not suggestive evidence of a tendency to thrombo-embolism. Hurn, Barker and Mann[6] found that the levels of antithrombin and prothrombin are often outside observed normals in patients having a tendency to thrombosis, but that high and low values are present in about equal numbers. Levy and Conroy[7] found decreased prothrombin times during ether anesthesia with a return to normal within 24 hours after operation. They used the bedside

TABLE I.—*Prophylactic Treatment of Thrombo-Embolism*
Comparison of Vein Ligation and Anticoagulants

Treatment	Number Patients	Thrombosis and Embolism	Fatal Embolism	Authors
None	302	11%	2.9%	Craaford & Jorpes
Heparin	352	0	0	
None	832‡	3.9%	0.7% (6 cases)	Edgar Allen et al.
Dicumarol	832	0.4% (3 cases)	0	
None	458*	12%	5.7%	
Vein ligation	458	1.1% (5 cases)	1 case	Arthur Allen

‡ Estimated Complications—Abdominal Hysterectomy.
* Selected Cases—Older Age Group.

method of determining prothrombin time. The work of Bancroft and Stanley-Brown[8] gives support to the thought that prothrombin activity may give a clue to thrombosis. They determined the "clotting index" according to the formula—C.I. equals $\frac{\text{Prothrombin} + \text{Fibrinogen.}}{\text{Antithrombin}}$ An index of 1.0 or over indicated a tendency to thrombosis and one of 0.3 or less, a tendency to bleed. In a series of postoperative patients, 65% had a normal clotting index and an uneventful convalescence. Thirty-five per cent had a high index and although no frank signs of phlebitis developed, this group all had fever and a prolonged convalescence without any demonstrable cause. Patients with phlebitis all had high indices as did seven patients with pulmonary emboli. They studied patients preoperatively and on the seventh and ninth postoperative days, and believed that a high index indicated a tendency to thrombosis. Shapiro[9] found hyper-prothrombinemia in patients who had venous thrombosis or a pulmonary embolus. He determined prothrombin time on diluted (12.5%) plasma as well as on whole plasma and found the most consistent decrease in the dilute plasma. His results using whole plasma were variable and at times he found increased prothrombin times when

thrombosis was actually present. He concluded that a decreased prothrombin time found with dilute plasma was an aid in the differential diagnosis of thrombosis. The data which are being presented indicate that an increase in the prothrombin activity of whole plasma precedes the appearance of clinical thrombosis although at the time when thrombosis is evident, the prothrombin activity may be normal or less than normal.

METHODS

The plasma prothrombin activity has been studied in two series of postoperative patients. In the first series of 73 patients, prothrombin activity was determined just before and within 6 hours after the operation, also daily until the sixth postoperative day. Patients selected for study were those in the older age group who were undergoing major surgery and those who had a previous history of phlebitis. All blood samples were drawn and the determinations were done by one of us (R. S.). In the second series the blood samples were drawn by the members of the surgical house staff or medical student externes on the first and second or third postoperative days. The determinations of prothrombin activity were done by one of three experienced technicians under close supervision. The method used for determining prothrombin activity is as follows, and is essentially that described by Quick.[10]

1. *Preparation of thromboplastin.* A fresh human brain is stripped of vessels, gross blood is washed off with normal saline, and the tissue macerated by beating at medium speed in an electric mixer. Water and lipids are extracted with large volumes of acetone at low temperature; usually four changes of acetone are required. The granular mass is filtered and then placed in a vacuum desiccator, and the acetone removed by an oil suction pump. The dry powder is kept in a desiccator under refrigeration. For use, 0.3 Gm. of the dry powder is suspended in 10 cc. normal saline and the mixture digested at 50-55° C. for 20 minutes with frequent shaking. It is then centrifuged at 1500 r.p.m. for five minutes and the turbid supernatant fluid pipetted off. This is mixed with an equal volume of .024 M calcium chloride solution and the mixture placed in a water bath at 37° C. just prior to use.

2. *Standardization of thromboplastin.* (Aggeler.[11]) Determinations are run in quadruplicate on two fresh plasma samples from each of five normal individuals. Prothrombin times of whole plasma and dilutions of 60%, 40%, 25%, 20%, 15%, 10% and 5% are determined and a curve constructed from the average values. Prothrombin activity of an unknown is calculated from this curve.

Different individuals may obtain dissimilar results because of differences in reaction time, so they must run checks against each other or carry out separate thromboplastin standardizations.

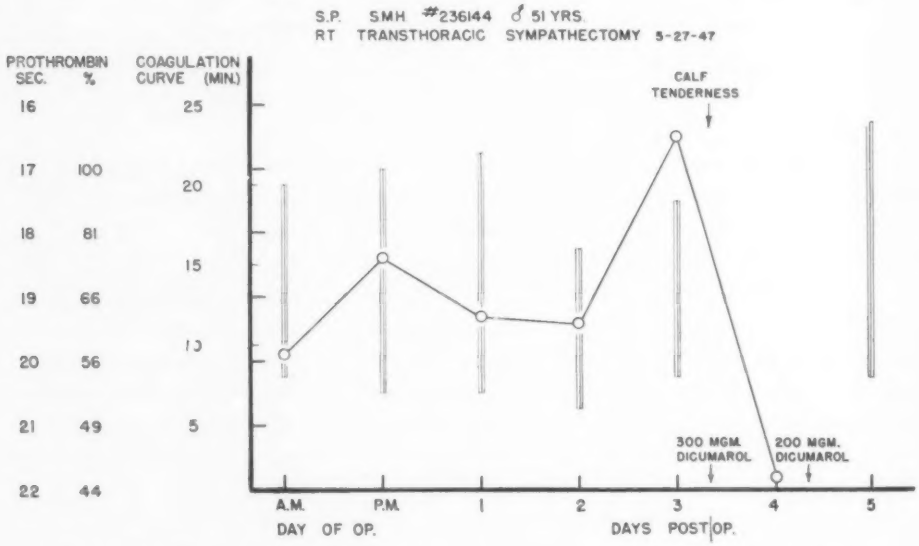
3. *Sampling.* Blood is drawn in a dry syringe, avoiding hemostasis as much as possible, and transferred to bottles containing dry oxalate mixture

(.006 Gm. ammonium oxalate and .004 Gm. potassium oxalate in 5 cc. blood). Hemolyzed or partially clotted blood is not used.

4. *Determination of prothrombin activity.* Blood is centrifuged at 2000 r.p.m. for 10 minutes and the plasma pipetted off. Determinations are run on whole plasma and on plasma diluted to 25% (1:3) with normal saline. 0.1 cc. plasma is pipetted onto a clean watch glass which is placed in the water bath at 37° C. To this is added 0.2 cc. of the thromboplastin-calcium chloride mixture; at this moment the stop watch is started. The mixture is stirred constantly with a glass rod; the end point is reached when clot formation is first observed. A black background facilitates observation of the end point. Determinations are run in triplicate.

OBSERVATIONS

The coagulation time in 20 postoperative patients was studied using the heparin-dilution method of Waugh and Ruddick.[4] Two of these patients

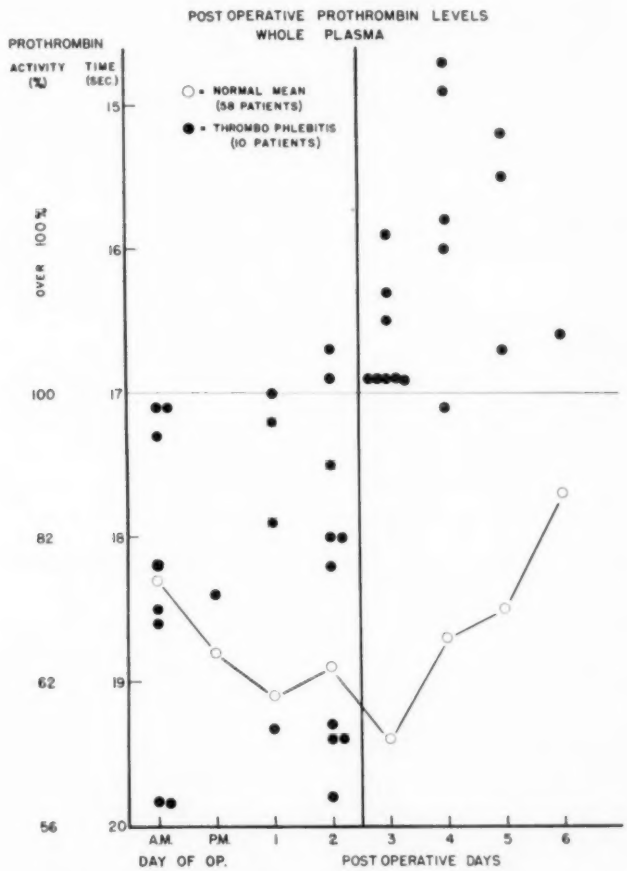


GRAPH 1.—Hypercoagulability in postoperative period, with concomitant rise in whole plasma prothrombin activity and subsequent thrombosis.

showed a decrease in coagulation time prior to the onset of clinically recognizable thrombosis; however, the procedure requires 15 cc. of blood, takes 30 minutes or more to complete, and the end point is difficult to standardize. At the same time, prothrombin activity of whole plasma was being determined in these patients, and Graph I shows the results in one which influenced us to concentrate on the study of prothrombin. This patient had a transthoracic sympathectomy for hypertension, and on his second and third postoperative days, the coagulation time was decreased. On his third postoperative day the prothrombin activity increased to over 100%, and late in

the afternoon minimal calf tenderness was noted. The following day the diagnosis of thrombosis of the leg veins was definite and he was treated with dicumarol.

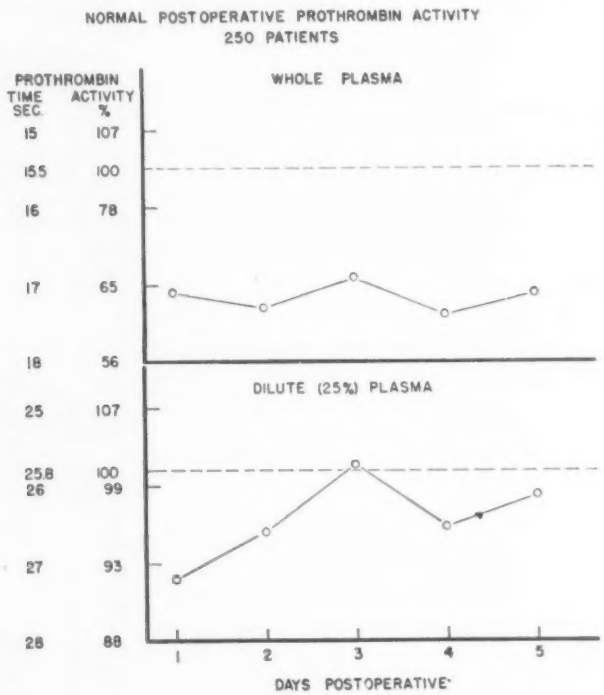
Graph II indicates the results obtained in the first series of 73 patients. Fifty-eight of the patients had no evidence of thrombosis during their postoperative course; the means of prothrombin activity of whole plasma are shown. (Graph II). There is a tendency for prothrombin activity to decrease



GRAPH II.—Hyperprothrombinemia in 10 patients who subsequently developed venous thrombosis. Black dots represent single prothrombin determinations. The remaining 5 patients in this series who showed hyperprothrombinemia received prophylactic dicumarol.

until the third postoperative day with a return to preoperative levels usually by the sixth day. This return to preoperative levels occurs sooner in young individuals. Ten of the first 73 patients studied developed definite venous thrombosis as a postoperative complication. Their prothrombin levels are indicated by the black dots (Graph II). There was nothing significant noted

preoperatively or on the first postoperative day, but two patients had levels above 100% on the second day and all were above 100% by the third day. None of these ten patients had signs of thrombosis on the second or third days, but all developed definite signs within the next three days. Five of these patients were treated with dicumarol and five were not. In some of



GRAPH III.—Mean normal prothrombin activity in 250 patients (second series).

the untreated patients, the prothrombin level remained high after the third day, but the levels may be normal or even below normal when thrombosis is clinically evident. The remaining five patients received prophylactic dicumarol because of hyper-prothrombinemia.

Postoperative prothrombin activity has now been studied in 382 surgical patients. The levels in patients who do not develop thrombosis correspond very closely with the results obtained in the first smaller series. The prothrombin activity of the *whole plasma* during the first five postoperative days has averaged 61 to 66 per cent (17.4 sec. to 16.9 sec.—15.5 sec. considered 100%)* (Graph III and Tables I and II). The prothrombin activity of *dilute plasma* varies between 92 and 101% during this same period. The mean values obtained and statistical analysis of these values are presented

* New thromboplastin of slightly greater potency was used for the determinations in the second series.

in Tables I and II. For statistical purposes, the levels on patients with hyper-prothrombinemia without clinical evidence of thrombosis are included with the control group. This tends to increase the coefficients of variation but these are still well within the probable limits of error of the method.

A summary of the 382 cases is outlined in Table III. There were 73 in the first series, and 309 in the second series. Three hundred and six

TABLE II.—*Postoperative Prothrombin Levels*
58 *Normal Patients*

	No. of Patients		Mean		Standard Deviation		Coeff. of Variation	
	100%	25%	100%	25%	100%	25%	100%	25%
Preop. (A.M)	56	50	18.3	32.2	1.25	2.82	.07	.08
Postop. (P.M.	20	13	19.0	36.7	1.78	2.31	.09	.06
Post-op. I.	27	21	19.1	35.4	1.27	3.94	.07	.11
Postop. II.	32	26	18.9	33.7	1.31	2.58	.07	.08
Postop. III.	17	12	19.4	33.3	1.31	2.20	.07	.07
Postop. IV.	24	19	18.7	32.0	1.27	2.43	.07	.08
Postop. V.	15	12	18.5	33.9	1.79	3.46	.10	.10
Postop. VI.	8	7	17.7	31.5	1.71	2.27	.10	.08

Whole Plasma 17.0 sec. = 100% activity.
Dilute Plasma 29.2 sec. = 100% activity.

patients or 80.1% did not have postoperative hyper-thrombinemia and did not develop thrombo-embolic complications. Sixteen patients developed thrombosis; all had hyper-prothrombinemia prior to the onset of clinical evidence of thrombosis. *No patient in this series who had been studied on the first and second or third postoperative days developed thrombosis without having had preceding hyper-prothrombinemia.*

TABLE III.

	Number	Mean Seconds	Standard Deviation	Coefficient of Variation
1st Day				
Whole Plasma	209	17.1	1.42	.083
25% Plasma	213	27.2	2.72	.10
2nd Day				
Whole Plasma	55	17.3	1.483	.086
25% Plasma	56	26.6	3.02	.114
3rd Day				
Whole Plasma	133	16.9	1.20	.071
25% Plasma	135	25.7	2.30	.089
4th Day				
Whole Plasma	45	17.4	1.48	.085
25% Plasma	45	26.5	3.16	.119
5th Day				
Whole Plasma	23	17.1	1.18	.069
25% Plasma	23	26.1	3.10	.119

Whole Plasma 15.5 sec = 100% activity.
Dilute Plasma 25.8 sec. = 100% activity.

Prophylactic dicumarol was administered to 41 patients in the series. Eighteen patients were started on the drug immediately after the operation because of a previous history of phlebitis or because of marked obesity or other factors which predispose to thrombosis. Twenty-three patients received prophylactic dicumarol beginning on the third postoperative day because of a sudden rise in prothrombin activity (whole plasma) on that day. We would have preferred to treat fewer of these patients in order to obtain

a more accurate evaluation of the test, but the various members of the surgical service were so convinced of the significance of the hyperprothrobinemia that they were unwilling to allow their patients to go untreated. One of these 23 patients received inadequate dicumarol therapy and had a non-fatal pulmonary embolus on the 11th postoperative day. None of the remaining 40 patients treated with dicumarol had any thrombo-embolic complication.

Nineteen patients who had a positive test on the third postoperative day did not develop definitely recognizable clinical evidence of postoperative thrombosis, and this group is worthy of careful analysis. There were 16

TABLE IV.—*Incidence of Postoperative Hyper-Prothrombinemia and Thrombosis*

	First Series		Second Series		Total	
	No.	%	No.	%	No.	%
Total Cases	73	100	309	100	382	100
Controls	56	76.7	250	80.9	306	80.1
Thrombosis (Total)	10	13.7	6	1.9	16	4.2
With hyper-prothrombinemia	10	13.7	6	1.9	16	4.2
Without hyper-prothrombinemia	0	0	0	0	0	0
Prophylactic Dicumarol (Total)	5	6.9	36	11.7	41	10.7
With hyper-prothrombinemia	5	6.9	18	5.8	23	6.0
Without hyper-prothrombinemia	0	0	18	5.8	18	5.7
Hyper-prothrombinemia Without thrombosis	2	2.7	17	5.5	19	5.0

males and 3 females. Seventeen patients of the 19 were out of bed on the first postoperative day, were made to walk and were not allowed to sit in a chair. The other two were made to exercise their legs. Ten of the nineteen had unexplained tachycardia and fever during the postoperative period, but because frank evidence of thrombosis did not develop, they are included in this group. It is probable that they had thrombosis, as many clinicians believe that unexplained tachycardia and fever are signs of venous thrombosis, and are adequate reason for vein ligation or anti-coagulant therapy. It is noteworthy that five of these 19 patients had surgery performed under tourniquets. Infection is known to cause hyperprothrombinemia and was present in two cases—one had lymphangiitis with periphlebitis and the other had peritonitis.

Ten patients in the control group of 306 came to autopsy; none had pulmonary emboli. During this same period, there were five other patients on the surgical service who died with emboli; four were the massive fatal type. None of these patients had been studied, as three had extensive metastatic carcinoma and the other two had surgery performed months before death.

DISCUSSION

The first series of 73 patients, which has been discussed in detail elsewhere,[12] was small and carefully controlled. Patients selected were those undergoing major abdominal or thoracic surgery, especially those with marked obesity or a history of previous thrombo-embolic disorders. It was

felt that if this test were to be of any value in the prediction of thromboembolism, it must be applicable to large numbers of patients under routine conditions. Therefore, a second series was studied comprising 309 unselected cases operated on between December 1, 1947 and March 31, 1948. Blood samples were drawn by the various house officers, subject to considerable variation in technique and time of day as regards meals, parenteral fluid administration, etc. Major surgical procedures of many types were included. Determinations were performed in a routine manner by one of three individuals accustomed to the procedure. As might be expected from the type of cases selected, the incidence of thrombosis in the first series was much higher than in the second; and the over-all incidence appears higher than is actually the case in this hospital because of the exclusion from both series of patients undergoing so-called minor procedures. The lower incidence of thrombosis in the second series is believed due to two factors: a wider selection of cases, and an increasing use of prophylactic dicumarol. In neither series did any patient on whom prothrombin levels were determined develop thrombosis without showing increased whole plasma prothrombin activity prior to the onset of symptoms.

The results obtained up to the present time indicate that the stage is set for postoperative thrombosis on the second or third postoperative days. This tendency to thrombosis can be detected by an *increased prothrombin activity of the whole plasma.* The prothrombin activity of dilute plasma shows greater variation and does not reflect the same characteristic change as is noted in the whole plasma. The determination of prothrombin activity on dilute plasma is generally considered the more accurate method by workers in this field, so it is possible that the change noted in whole plasma is due to some factor in the clotting mechanism other than prothrombin. Further investigation will be required to settle this point. The hyperprothrombinemia which has been found in patients who develop thrombosis occurs before the diagnosis can be made by clinical examination and is present early in the postoperative period (second or third postoperative day). When thrombosis has become definitely established, the prothrombin activity may be normal or even diminished. It is possible that the hyperprothrombinemia reflects beginning thrombosis in the small veins of the foot or calf or about the operative site. It has been present in patients who later developed either superficial or deep thrombosis.

The data presented are not sufficient to permit sweeping conclusions, nor do we believe that the test is 100% accurate in all surgical patients. No patient has been studied who developed thrombosis without preceeding hyperprothrombinemia, but not all patients who had a positive test developed clinical evidence of thrombosis. It is possible that many of this latter group did have thrombosis which was not clinically detectable or that the tendency to thrombosis suggested by increased prothrombin activity was overcome by early mobilization, active leg exercises, and other preventive measures. The

hyperprothrombinemia in patients who had tourniquets used in surgery of the extremities is of interest, and this feature is now being studied.

At the present time we feel that all patients showing hyperprothrombinemia on the second or third postoperative day are candidates for thrombosis, and unless there are definite contraindications, these patients receive prophylactic dicumarol without any other modification of the postoperative routine. It does not seem necessary to reduce the prothrombin to dangerously low levels when dicumarol is being used prophylactically. Heparin is used in the treatment of definite thrombosis until an adequate dicumarol effect is obtained. Vein ligation has not been used in this series of patients, but hyperprothrombinemia might be considered as an indication for ligation by advocates of this method of therapy. Our experience with this test is limited to patients who are not confined to bed for long periods following surgery. No data have yet been obtained on patients immobilized for long periods in traction.

CONCLUSIONS

1. A definite increase in prothrombin activity of whole plasma on the second or third postoperative day appears to be a warning of impending venous thrombosis.

2. Postoperative hyperprothrombinemia is a valuable test in determining which patients should receive prophylactic measures against thrombosis.

3. Administration of dicumarol when the hyperprothrombinemia develops is effective prophylaxis against thrombo-embolic complications.

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Discussion.—Dr. Frederic W. Bancroft, New York: I am intensely interested in the work Dr. Mahoney has done, because since 1928 I have been interested in the problem. Dr. Stanley-Brown and I, as many of you know, had worked out a clotting index. In our original series we had about 1600 routine examinations of pre- and postoperative patients, in which we took the values preoperative, five days postoperative and nine days postoperative. We should have made this five-day examination earlier, as Dr. Mahoney has shown. We early dropped from our list the antithrombin, which we felt was of no importance. We did prothrombin and fibrinogen determinations during the latter part almost entirely depending on the prothrombin test. It was not as accurate as that which Armand Quick developed for us at the Fifth Avenue Hospital.

In our series we have had no accidents in those that did not have a high prothrombin content. We did have something similar to what Dr. Mahoney stated; a certain percentage that had high prothrombin times but did not develop external signs of thrombosis. However, in reviewing the charts we would universally find that they ran a higher postoperative temperature than the average case. No one in the low prothrombin group developed accidents. We had at that time the opportunity to examine a lot of patients throughout New York city who had embolic accidents, and all had high prothrombin after the accident with the exception of one case; that was an amputation of the breast, and there was definitely thrombosis of the bacillary vein and emboli in the lungs. I feel that if we can develop first, an idea of the type of patient that is going to develop thrombosis, and give that patient prophylactic therapy, we will do much better than if we ligate a lot of veins or if we overdose a lot of people with dicumarol or heparin, who probably don't need it, and which raises the patient's expense. If we can analyze our cases, or get our danger gauges, if only a few hours before the first physical signs appear, I think we will have made a great step forward, and I want to thank Dr. Mahoney for his excellent paper.

Dr. Walter D. Wise, Baltimore: At a meeting of the Southern Surgical Association in 1946, the statement was made that at Mercy Hospital, Baltimore, we had introduced the prophylactic use of dicumarol in postoperative cases, and that in a rather large series we had had a reduced incidence of thrombo-embolic cases and no deaths. This preliminary report was made with hesitation for fear it would be considered not quite within the realm of fact. We now wish to quote larger figures over a longer period of time and feel more secure in doing so, after noting such statements as those of Barker and his group, the paper today and many other recent articles. Dicumerol has been used in our work because it can be used orally, is easier to regulate than heparin, and is far less expensive. Of course when a quick change is needed we use heparin. The prophylaxis program in actual practice includes various types of surgery, but for purposes of presentation and discussion the category where predisposition to thrombo-embolic complications is most likely, in major pelvic and abdominal surgery, or combinations, has been selected. The number for the period 1944-47 inclusive seems sufficiently significant for comparison and formulation of tentative conclusions. It must be said, however, that larger numbers are most desirable, as well as a longer period of time before definite conclusions can be drawn

For the four-year petriod, 1944-45-46-47, there was a total of 5335 major abdomino-pelvic operations; 2330 cases were untreated, that is, they were not tested nor treated, with 25 thrombo-embolic complications, 9 embolic phenomena and 6 deaths from pulmonary embolism. There were 3304 cases treated prophylactically with dicumarol, with four thrombotic complications, one pulmonary infarction and one death, probably not actually due to pulmonary embolism. This patient had carcinomatosis with extensive involvement of the liver. She died after being in a comatose state for five days. There were no clinical symptoms of pulmonary embolism, but one was found at autopsy. She did not have dicumarol for about a week.

ENDOTHELIOMA OF BONE
(Ewing's Sarcoma)

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INTRODUCTION

There exists a specific type of malignant bone tumor, now designated as Endothelioma or Ewing's sarcoma, which has justified its consideration as a disease entity by reason of its characteristic age incidence, clinical course, therapeutic response, prognosis and the accumulation of a reasonable number of acceptable cases. While the opinion of pathologists may be divided concerning the exact nature or origin of this lesion there now seems to be general agreement as to its distinct cytological features.

By earlier pathologists this tumor was undoubtedly classified with the heterogeneous and inclusive category "round cell sarcoma". In 1866 Lucke[50] first described a primary bone tumor resembling endothelioma. Other reports followed and, in America, Howard & Crile[39] reported 23 cases in 1905, four of which had been personally observed. Ewing revived interest in the condition in 1921[23] and did much to enhance our knowledge of it and to establish it as an important clinical entity.[24]

GENERAL DESCRIPTION

Though a relatively rare disease, Ewing's sarcoma occurs more frequently than any other primary malignant bone tumor except osteogenic sarcoma. It is an affection of childhood and adolescence with males afflicted twice as often as females. Arising in the medullary or subcortical portion of both long and flat bones and characterized by destruction rather than by production of bone, it later forms bulky swellings of the soft parts overlying the area of involved bone which often assumes a fusiform shape.

Pain is predominately the first symptom of the onset of the disease and disability follows early and progresses proportionately. The onset is often insidious and early symptoms and signs may simulate a pyogenic infection of bone. Progress of the disease is quite variable, being very rapid in some cases while in others a fatal termination may be long deferred. The disease tends to metastasize not only to the lungs as in osteogenic sarcoma, but also to other bones, particularly the skull.

The tumor shows marked radiosensitivity which may be a delusion for, while the early response to roentgen-rays may be most encouraging, the later complications of local recurrence and metastases are most discouraging fea-

* Read before the American Surgical Association, Quebec, Canada, May 28, 1948.

tures. The end results, expressed in terms of 5-year recoveries, are extremely poor.

MEMORIAL HOSPITAL SERIES

Because of the paucity of published information concerning this tumor, it seems desirable to report the experience of the Bone Tumor Service of Memorial Hospital. During the thirty-year period from 1918 through 1947, there have been admitted to this clinic 179 patients with a tentative diagnosis of Ewing's sarcoma. Some of this group were so classified on the basis of clinical findings alone and others on the basis of clinical and roentgenographic findings only. These have been excluded from our analysis along with some cases with tissue specimens for histologic study in which the original opinion has not been sustained but changed, on critical analysis and review, to reticulum cell sarcoma, neuroblastoma, metastatic carcinoma, eosinophilic granuloma, etc.

Of the original 179 there remain 91 cases with histologic proof that is acceptable to our pathologist on recent review.* These 91 cases have been selected for detailed analysis and form the basis of this report. Twenty-seven of this group have been registered with the Bone Sarcoma Registry of the American College of Surgeons and have been classified by them as Ewing's tumor.

For the determination of prognosis and end results only the 73 cases admitted between 1918 and 1942 are considered in order to allow for the lapse of a minimal interval of 5 years in determining survival rates.

ETIOLOGY

Sex. The general belief that males are afflicted about twice as frequently as females is supported by study of our 91 cases in which 63 or 69% were males and 28 or 31% were females. (Chart I.)

Age. In the present series ages range from 5 months to 36 years, with an average age of 15 years for the group as a whole. In the 63 male patients the average age was 16.1 years and in the 28 females it was 12.4 years.

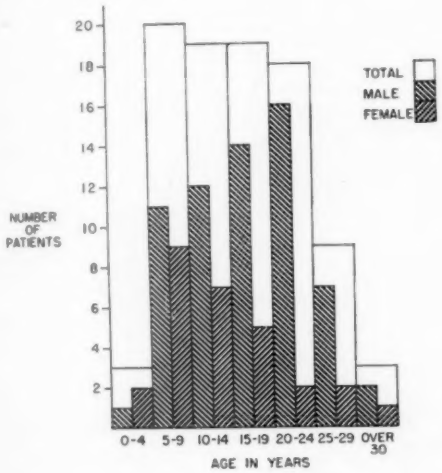
It is readily apparent from Chart I that the peak incidence of Ewing's sarcoma is in childhood and the adolescent years. It is striking that in only four cases of the entire series was the patient 30 years of age or older at the time of onset of symptoms, and that the oldest patient was only 36 years old. It is our belief that a diagnosis of Ewing's sarcoma in a patient over 35 years of age is open to question on the basis of age of the patient alone.

Trauma. An occasional case of malignant bone tumor is reported from time to time in which trauma appears to have been a significant etiological factor. It is probable that trauma in many instances focuses the attention of

* The authors are deeply grateful to Dr. Fred W. Stewart and Dr. Frank W. Foote for reviewing the microscopic pathology in all the cases included in this study.

physician and patient alike on a bone already harboring a tumor, a circumstance referred to by Ewing as traumatic determinism, and it is incorrectly assumed to be the cause of the lesion. In fact, it is seldom that all of Segond's six postulates[69] in establishing a traumatic relationship are satisfied in any given case and the postulates are not adequately satisfied in any of the cases in the present series.

In 41 cases of this series there is no recorded information concerning the presence or absence of trauma and in 15 others trauma was specifically denied. Of the remaining 35 cases, seven alleged that a fall on, or a blow to, the part initiated symptoms after a short interval, while in 12 there was an interval of from two months to seven years between the alleged injury and the onset of symptoms. The described injury was vague or indefinite as to manner incurred and as to time relationship to the onset of symptoms in 16 cases. (Table I.)



AGE AND SEX INCIDENCE OF 91 CASES EWING'S SARCOMA

CHART I.

Infection. In his original description of this disease Ewing remarked on the presence of an associated or antecedent febrile illness. Subsequently he expressed the view that if the theory of the bacterial cause of cancer had any foundation in fact then endothelioma (as well as lymphosarcoma) should provide the most fertile field for discovery or proof. We share this premise and are inclined to the belief that some obscure infection, perhaps virus in nature, may be found to be a factor in the development of Ewing's sarcoma. It is a common observation that the early signs and symptoms of Ewing's sarcoma suggest an underlying infectious process and Connor,[15] in a review of the registered cases, reported 40% with a distinct history of early signs pointing to inflammation as an etiologic factor. He further showed that the histologic appearance of tissue seen in these cases may be indistinguishable from inflammation of bone. Meanwhile the actual causative factors of this form of bone sarcoma remain completely obscure.

An associated infection was noted in the history of 11 of our cases. There were three upper respiratory infections, two sore throats and three exanthemata.

ANATOMIC SITE

The site of the primary tumor is known in all 91 of our cases. Reference to Figure 1 will disclose the frequency with which the various parts of the

skeleton were involved in this series of cases. It will be seen that the femur, the primary site in 23 cases, was the most frequently involved bone. The bones of the skull and face, the carpal bones, the metacarpal bones, the ischium, and the phalanges were in no case the site of primary bone involvement. Bones of the right side of the body were involved primarily in 48 cases, those of the left side in 40 cases, the sacrum being the only unpaired bone found as a primary site in the remaining three cases. The bones of the

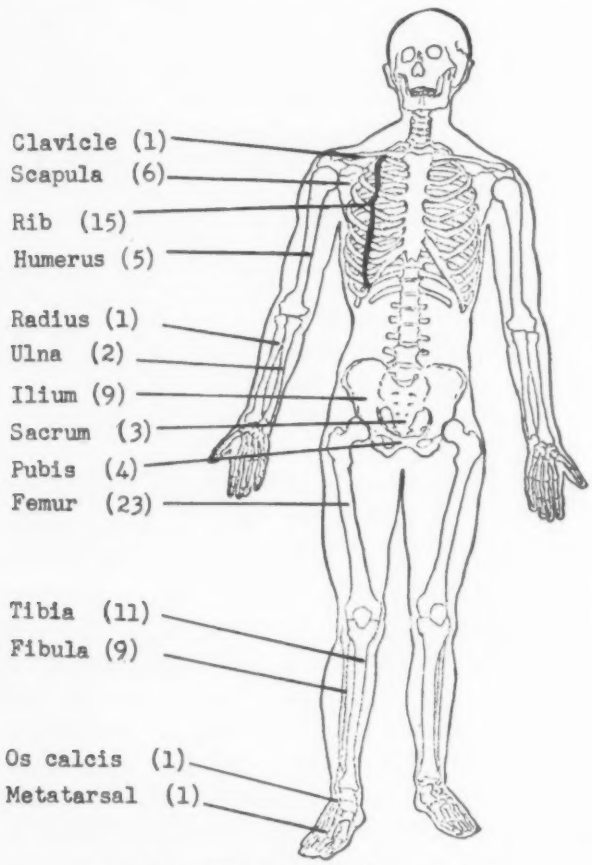


FIG. 1.—Anatomic site of primary lesions.

upper extremity were primarily involved in 15 cases, the bones of the lower extremity in 45 cases, and those of the pelvic girdle in 16 cases. All of the ribs except the first, second, and twelfth were, in one or more cases, the site of the original tumor in a total of 15 cases.

SYMPTOMS

Ewing's sarcoma differs little from other malignant bone tumors in symptomatology. Pain, swelling and disability constitute the major triad and, in Ewing's sarcoma, fever may be an important additional symptom.

(Table II.) A review of the present series merely emphasizes the well recognized importance of pain, and especially pain at rest, as an indication of the presence of an expanding bone lesion and supports our admonition that persistent pain in any bone calls for a tentative diagnosis of a malignant bone tumor and thorough investigation of the case clinically, roentgenologically and histologically.

Pain. Because of deplorable incompleteness of the medical records, no statement as to the presence or absence of pain is made in 13 of the 91 cases. However, 74 patients complained of pain in the affected part, and six of these offered this as their only complaint at the time of their first visit to the clinic. Pain was usually described as aching or boring in character and not particularly relieved by rest. Severity varied considerably from a seemingly mild degree to such intensity as to require opiates for relief. The

TABLE I

Antecedent trauma in 91 cases of Ewing's sarcoma

		No. of patients
Trauma specifically denied		15
No statement as to trauma		41
Antecedent trauma recorded		35
Definite trauma at onset of symptoms	7	
Definite trauma with stated interval	12	
Indefinite trauma	16	
Total		91

TABLE II

Symptoms in 91 Cases of Ewing's Sarcoma

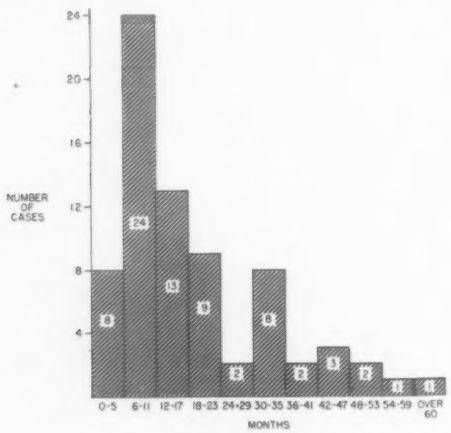
	Present	Denied	Not Stated
Pain	74	4	13
Deformity or swelling	63	3	25
Disability	31	5	55
Fever	15	7	69

severity appeared to depend upon the location of the lesion, involvement of contiguous structures, the presence of pathologic fracture, or the individual threshold for pain. In only four cases was pain specifically denied. But of the 74 patients complaining of pain 43 described it as their first symptom and 21 mentioned it secondarily to some other initial symptom—notably swelling (Table II.) In general pain is worse at night, is unrelieved by rest and, while it may be intermittent in the earliest stages of the disease, rapidly increases in persistence and severity.

Swelling. If swelling is not the initial symptom, it usually follows the onset of pain promptly and in proportion to the amount of pain. In this series 63 patients complained of tumefaction in the affected part, three noticed no swelling or deformity, while in the remaining 25 case records no statement is made relative to a complaint of swelling. (Table II.) Swelling was the only complaint in six cases, 18 patients described it as their initial symptom, while 17 patients noticed swelling coincident with other symptoms —usually pain.

Disability. With most bone tumors disability, or loss of function, is a common secondary complaint. However, the disability appears early in Ewing's sarcoma and increases in proportion to the degree of pain and swelling which, *per se,* produce the disability. The pain resulting from movement of muscles and tendons over the tumor contributes to the disability which is enhanced by the protective mechanism of neighboring joints seeking to maintain the physiologic position of rest. A patient suffering the type of pain characteristic of this disease will invariably favor the affected part and will accordingly experience loss of function.

All but two of the 31 patients complaining of loss of function had primary involvement of the bones of the pelvis or lower extremity so that disability in walking or standing was complained of as might be expected. Two patients had a pathologic fracture to account for their disability when first seen in the clinic.



SURVIVAL BY HALF-YEARS FROM TIME OF DEFINITIVE TREATMENT TO DEATH

CHART II.

Fever. As a subjective complaint fever, with or without chills, was noted in 15 of the 91 cases, it was specifically denied in seven cases and was uncertain or not stated in the remaining 69 cases. (Table II.) A rib was the primary site of involvement in six patients who complained of fever and in three of these fever was the only complaint on admission to the clinic. Subsequent febrile attacks were not uncommon and, in a treated case, may be the first warning of local recurrence or metastasis.

Miscellaneous. Numerous and variegated concomitant complaints are to be anticipated in a highly malignant tumor of this nature and depend largely upon the site of the primary tumor. Thus, symptoms of cough, shortness of breath, chest pain and voice change were presented in cases with primary rib involvement and are to be expected in patients with pulmonary metastases. Anorexia was complained of by two patients and 19 patients mentioned weight loss varying from two to 40 pounds over time intervals varying from two months to two years. Loss of weight is not unusual with any patient harboring a malignant tumor. It should not be regarded as an early symptom, and is more apt to ensue from lack of sleep and loss of appetite resulting from pain and disability than from actual tumor growth.

PHYSICAL FINDINGS

In the local examination it is important to note the color and texture of

the overlying skin, the presence of local heat or tenderness, the existence of a palpable tumor and its mobility in relation to the bone and the position of rest assumed by the patient to obtain maximum comfort. The complete general examination should include a search for involved lymph nodes, bone or soft part metastases, and recording of clinical temperature in addition to the laboratory studies described below.

Several of our cases had received preliminary treatment elsewhere so that a description of the early findings was not always available. However, data sufficient to be of statistical value were obtainable in 86 of the cases.

Palpable Tumor. Of the 86 cases in which some information is provided 54 patients presented a palpable tumor and nine presented no demonstrable tumor or swelling in the affected part. Of the remaining 23 patients 14 had been treated surgically elsewhere (amputation or resection) and nine had been treated with roentgen rays or radium and no palpable tumor was found on admission to this clinic. The tumor was described as being discrete, regular, smooth and fusiform in shape in 12 cases, as nodular in three cases, and diffuse or indefinite in five cases. The consistency of the tumor was variously described as being firm, moderately hard or bony hard in 38 cases and as soft and fluctuant in three cases. (Table III.)

TABLE III

Physical Findings in 91 Cases of Ewing's Sarcoma

	Present	Absent*	Not Stated
Palpable tumor	54	32	5
Tenderness	15	19	57
Local heat	6	4	81
Local redness	2	7	82
Temperature elevation	52	30	9
Limitation of motion	12	7	72

It should be borne in mind that actual bony swelling due to tumor growth is usually noted early but may be masked by an attendant soft part atrophy of disuse due to disability. Thus inspection and circumferential measurements might be misleading but careful palpation will frequently reveal the existence of actual bone enlargement or swelling.

Tenderness. Local tenderness was elicited in 15 patients of this series. It was specifically absent in 19 patients and no comment was made regarding tenderness in the remaining 57 patients.

Local Heat and Redness. In this series local heat was present in six cases and absent in four. Local redness was described in two patients and absent in seven. No mention is made of the presence or absence of these findings in the remaining cases. In view of the fact that Ewing's sarcoma may resemble acute infection of bone, the evaluation of the findings of local tenderness, redness and heat may have considerable significance in the differential diagnosis and, while sometimes present in Ewing's sarcoma, they are not apt to be as marked as in inflammatory lesions.

(* Note: 23 patients had previous treatment elsewhere and might be expected to have altered physical findings.)

Limitation of Motion. In any painful lesion of bone considerable voluntary limitation of motion is to be expected. The limitation, however, is seldom if ever mechanical as actual joint involvement is rare even with extensive disease. In 12 of our cases it was noteworthy while in seven cases there was no limitation. No mention is made regarding this finding in the other 72 case records.

Fever. The presence of an elevated temperature in Ewing's sarcoma is frequently enough encountered to warrant its consideration as an important physical sign. It may occur with the onset of symptoms when the temperature chart may closely resemble that of an acute inflammatory process in bone or it may be the first and only sign of local recurrence or metastasis. A temperature elevation above 100° F. was observed in 52 patients in our series during their hospitalization. Of these there were 27 who presented various complications such as fungating wounds, cord bladder, pulmonary metastases, etc., which, of themselves, might account for the elevated temperature. There was no obvious explanation for the elevated temperature in the other 25 cases other than the tumor itself. Thirty patients had no recorded temperature above 100° F. during their hospital stay although 5 of them complained of chills and fever, and there is no record of the temperature in the 9 remaining cases who were never hospitalized.

FIG. 2. — Roentgenographic appearance of early subcortical lesion of Ewing's sarcoma of the left ulna in a 17-year-old female.

LABORATORY FINDINGS

Roentgenographic. Ewing's sarcoma is generally believed to present a characteristic roentgenographic appearance. The classical findings are those of an osteolytic lesion of bone irregular in outline, apparently of central or subcortical (Fig. 2) origin and rapidly involving the entire circumference when arising in a tubular bone (Fig. 3). There is "onion-peel" appearance of the overlying periosteum which is due to reactive bone formation rather than tumor invasion and imparts a fusiform shape to the tumor. Later there may be an associated soft part involvement visible on the roentgengram.

This typical appearance is not always found and was noted in only 12 of the patients in this series while a close resemblance was described in 12 additional cases. In 16 cases the roentgenogram of the early initial lesion was unavaliable or unsatisfactory for interpretation. In the remaining 51 cases the report on the roentgenographic examination was non-informative

or the appearance more closely resembled some other condition such as osteogenic sarcoma, reticulum cell sarcoma, inflammatory disease, etc. (Fig 4a.)

The diaphysis of long bones is usually the primary site of involvement but occasionally the metaphysis may be the site of origin. A study of the early roentgenograms available in 45 cases in which the tubular bones were involved revealed origin in the diaphysis in 37 cases (82%) with early spread of the disease to the metaphysis in 8. The disease began in the metaphysis in

FIG. 3.—Classical appearance of Ewing's sarcoma involving the upper shaft of the femur in a 27-year-old male.

8 cases (18%) with early spread to the diaphysis in 1 case. Later in the course of the disease nearly the entire bone may become involved.

Atypical and varied findings are to be expected in the flat bones (25% of the cases) and even in the long bones unusual and bizarre appearances may present themselves to the extent that pathologic examination is necessary to establish a diagnosis (Fig. 4a).

Blood Studies. The blood levels of calcium, phosphorus and phosphatase are always desirable in the evaluation of bone lesions. In Ewing's sarcoma

these values are seldom abnormal. In the late stages of the disease with rapid and extensive bone destruction the calcium might be elevated. If pathologic fracture has occurred some rise in phosphatase may occur as a result thereof although a slight elevation in the phosphatase level may be found in Ewing's sarcoma.

Serology should also be obtained in all patients with a bone tumor as syphilis is protean in its manifestations and may resemble any type of tumor particularly Ewing's sarcoma. Serologies were recorded in 27 of our cases and were negative in every instance.

FIG. 4. (a.) — Ewing's sarcoma of the right tibia in a 30-year-old male. Unusual roentgenographic appearance resembling fibrous dysplasia or reticulum cell sarcoma.

Because Ewing's sarcoma may resemble inflammatory bone disease in many instances the white blood count may have considerable significance. While leukocytosis may occur it is not as apt to be as marked in Ewing's sarcoma. In our series of 91 cases white cell counts are recorded in 67 and a total white cell count in excess of 10,000 was present in only 26. Some of these elevations in cell count might well have been due to coincident conditions such as infected or fungating wounds, pulmonary metastases with pneumonitis, etc. However, 12 of the 26 patients, or 18% of the 67 cases, presented no recognized cause for the leukocytosis other than the presence of the tumor. In these cases the leukocytosis varied from 10,000 to 13,800 with no significant variation in the differential count.

Histology. Aspiration biopsy, or, if necessary, formal biopsy prior to any form of therapy is necessary in all cases to establish the diagnosis beyond all doubt. All 91 cases in this series had pathologic examination of representative tissue and have been classified by the pathology department of Memorial Hospital as Ewing's sarcoma.

The histologic picture of these cases is that of a neoplasm showing, in areas, crowding of cells in broad sheets and, in other areas, relatively few cells surrounded by a loose, often vacuolated, cytoplasm, often with areas of necrosis, degeneration and hemorrhage. Cells may occasionally be seen in pseudo-rosette arrangement. The cell itself is characterized by a round or ovoid nucleus with one or more nucleoli and frequently a poorly delimited cell membrane. Leukocytic infiltration is common and is sometimes of such a degree as to obscure the true underlying neoplastic nature of the lesion (Fig. 4b).

DIAGNOSIS

Ewing's sarcoma may simulate other malignant bone tumors as well as certain non-neoplastic lesions of bone. Of the former, the most important are osteolytic varieties of osteogenic sarcoma (Table IV), reticulum cell sarcoma of bone and metastatic neuroblastoma. The roentgenographic findings are significant. Those characteristic of this type of tumor are extensive involvement of the shaft, and irregular cortical destruction associated with subperiosteal reactive new bone formation, giving rise to the laminated or "onion skin" appearance. This picture in some instances may be closely approximated by osteomyelitis; in fact the diagnostic difficulty is increased when fever and leukocytosis are present. Eosinophilic granuloma in its early stages may also offer difficulties in roentgenographic interpretation although the symptoms here are usually milder and the bulky soft-part tumor is lacking.

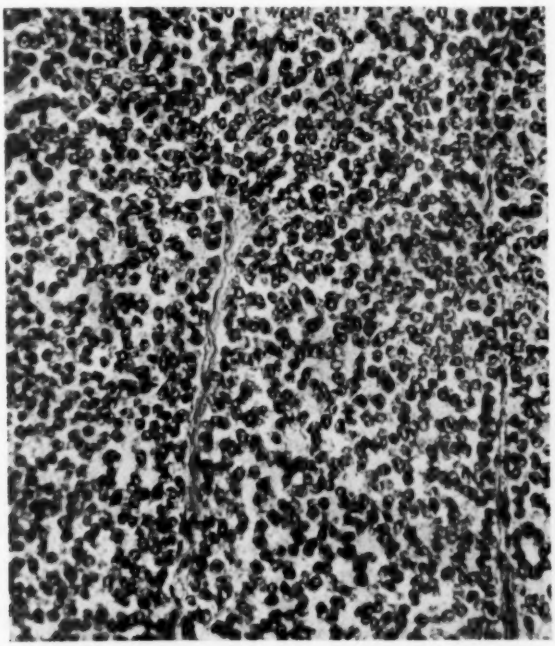


FIG. 4. (b.)—Same case. Characteristic microscopic appearance of Ewing's sarcoma.

TABLE IV

Roentgenographic Differential Diagnosis between Ewing's Sarcoma and Osteogenic Sarcoma

Ewing's Sarcoma	*Osteogenic Sarcoma*
1. Location—usually in diaphysis	1. Location—usually in metaphysis
2. Expands shaft	2. Fails to expand shaft
3. Extent—usually more than half the length of the bone	3. Extent—involves less than half the bone
4. Osteolytic	4. Usually osteoblastic
5. New bone is reactive and laid down parallel to the long axis of the bone	5. New bone is largely "tumor bone" and is laid down irregularly often radiating at right angles to the long axis

Owing to the difficulties of establishing a diagnosis based on clinical and roentgenographic criteria alone, we feel that every suspected case should have microscopic confirmation. Furthermore, since even mild exposures to roentgen rays may result in an incorrect and totally misleading histologic interpretation, we would emphasize the importance of performing the biopsy prior to the use of roentgen therapy. So highly radiosensitive is this tumor that even mild exposures will obliterate all recognizable features of the lesion and change the picture to one suggestive of inflammatory or necrotic tissue (Fig. 5).

While there is as yet no universal acceptance of the principle of aspiration biopsy as a means of affording material for histologic study, it is worthy

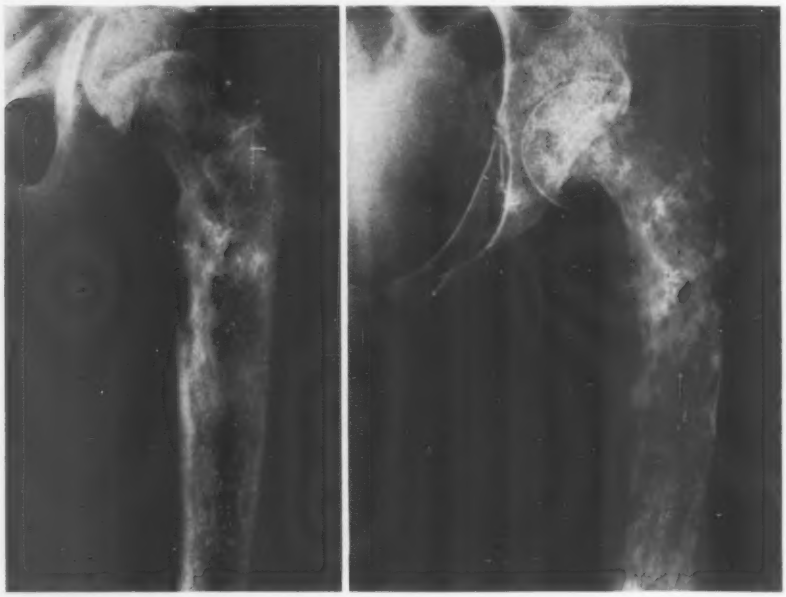


FIG. 5. (a.)—Destructive lesion in upper end of left femur in a 12-year-old female. Biopsy after radiation therapy had been started was interpreted as chronic osteitis. (b.) Unusual course of the disease prompted a second biopsy 1½ years later which revealed Ewing's sarcoma. Patient died of multiple metastases six months after the second biopsy.

of note that this method has proved most successful in establishing the diagnosis of Ewing's sarcoma. In 42 cases of this disease[73] in which it was employed, the pathologist was able to make a specific diagnosis in 31, and to report six additional cases as malignant tumor. We must concede, however, that in most clinics a biopsy by direct surgical approach will afford a safer means of identifying the suspected lesion. If a surgical biopsy is performed the wound should always be closed in layers without packing or drainage. Should one encounter material that is suggestive of pus, cultures should be taken but the possibility of Ewing's sarcoma should not be excluded until sections have been studied by the pathologist.

TREATMENT

Two patients in this series, after examination and diagnosis, were referred back to their own physicians; the remaining 89 cases received some form of therapy at Memorial Hospital. In most instances more than one therapeutic agent was employed. These will be considered in turn, and the comparative value of the various methods will be discussed with the end results.

Surgery. In this series of 91 cases 115 surgical procedures were carried out. The majority of these were incision and drainage (performed under the mistaken diagnosis of osteomyelitis), open biopsies, and aspiration biopsies, and were employed for purposes of diagnosis rather than for therapy. There were, however, 33 definitive surgical procedures performed in an effort to eradicate the tumor; these comprised 18 amputations and 16 segmental or partial resections.

Roentgen therapy. In this series, 69 patients received roentgen therapy to the primary tumor. Since there have been many changes and advances in this field in the past thirty years, the treatment administered in each individual case naturally reflects the equipment and technic in vogue. Thus the early cases were treated empirically in terms of time of exposure to beams of unknown intensity. The majority, however, were treated with multiple converging ports and fractionated doses with high voltage machines (200 KV or 250 KV), usually at target-skin distances of 50 or 70 cm. The size and number of the ports varied with the particular lesion being treated. It is impossible to state with any degree of accuracy the total skin doses thus administered. Furthermore, it is the tissue (or tumor) dose which is the important factor to consider and this could not be estimated from the data available. Only one patient received 1000 KV therapy.

The initial response of the lesion, when recorded, was in every instance clinically gratifying and serial roentgenograms revealed evidence of bone regeneration in most cases.

Radium. Radium was administered in 32 cases. This was usually in the form of surface irradiation from a 4-Gm. radium element pack placed at 6 to 10 cm. distance, the size and number of the surface portals varying with the particular lesion being treated. In two cases gold filtered radon seeds were inserted into the tumor, and another patient received small quantities of radium chloride intravenously. The clinical response in most instances was similar to that obtained with roentgen therapy.

Toxins. Fifty-five patients in this series received one or more courses of Coley's Toxins (the mixed toxins of erysipelas and Bacillus prodigiosus, Shear's filtrate, etc.). A course usually consisted of from 10 to 12 intramuscular and intravenous injections beginning with a dose of a fraction of a minim and progressively increasing in accordance with the patient's response to each injection. No one in this series was treated with toxins alone. From the data available it is difficult to evaluate objectively the exact effect

of the toxins on the disease but it is our belief that Ewing's sarcoma is one type of malignant neoplasm that shows a favorable response to Coley's toxins when used in conjunction with other therapeutic agents.

Miscellaneous. In the earlier years covered by this series one patient was treated with intravenous injections of colloidal lead, and in later years three patients received small quantities of radioactive phosphorus. In each instance these medications were employed experimentally and in conjunction with other methods. No unusual benefits were noted.

FIG. 6. — Pathologic fracture through primary Ewing's sarcoma of the femur 8 months after radiation therapy had been instituted. High thigh amputation was done but patient died with multiple metastases 10 months after amputation.

Pathologic Fracture. The occurrence of pathologic fracture in Ewing's sarcoma has not been emphasized by most writers. As with any osteolytic lesion of bone this complication might be expected to occur not infrequently. In the present series of 91 cases a pathologic fracture occurred in 19 or 21 per cent. Six of these had occurred shortly before the time of admission or were discovered at the actual time of admission. In 14 of the 19 cases the pathologic fracture occurred through the site of the primary bone lesion (Fig. 6) while in the remaining five it occurred at the site of osseous metastasis from a primary lesion elsewhere. Only one pathologic fracture was encountered in the humerus. The remaining 18 all occurred in the bones of the spine, pelvis, or lower extremity where weight-bearing probably served as a precipitating factor. The incidence of pathologic fracture and the bone involved is recorded in Table V.

Local Recurrence. In this series there were 18 patients who presented either a microscopically confirmed, or clinically unequivocal, recurrence at the site of the primary lesion from two months to three years following the institution of therapy to the primary lesion. An analysis indicates that in eight cases the recurrence may have resulted from an inadequate dose of roentgen rays or radium. This statement is made after a very rough approximation of the amount of irradiation apparently administered to these eight patients plus a comparison of these values with the arbitrary values determined by Woodard and Coley[85] for the sterilization of Ewing's sarcoma. Judging by the same standard five of the remaining patients seem to have had an adequate tissue dose administered but the skin portals are believed to have been inadequate to cover the entire extent of the underlying tumor. The last 5 patients in this group seem to have had local recurrences as a

result of inadequate surgery; two had simple rib resections instead of chest-wall resection for tumor of a rib, two had high thigh amputation and one had a mid thigh amputation for tumor of the femur, instead of hipjoint disarticulation.

Neurologic Disorders. As a result of cerebral or spinal metastases neurologic disorders occurred with sufficient frequency to warrant discussion as a separate, frequent complication. Fifteen patients (16 per cent) of this series had objective evidence of a neurological lesion at some time during the course of their illness. Two patients with primary Ewing's sarcoma of the sacrum had symptoms and signs of sacral root involvement evidenced by urinary retention, constipation, and lower abdominal or leg pain. Eight patients had complete paraplegia believed to be due to a transverse myelitis

TABLE V

Pathologic Fracture in 19 *Cases*

(series of 91 cases of Ewing's sarcoma)

Bone Involved	Cases	
Femur	10	(one metastatic)
Vertebra	3	(all metastatic)
Tibia	2	
Rib	2	
Humerus	1	(metastatic)
Pubis	1	
Total	19	

in the dorsal cord produced by metastasis. One of these patients also had loss of vision and an ophthalmoplegia, another had a right facial paralysis in addition to his paraplegia, and another had facial paralysis and inability to swallow. One patient developed a quadriplegia. The remaining two had urinary retention with episodes of incontinence believed to be due to lower cord metastases. All of these patients were, of course, in the terminal phase of their disease and none survived for long.

Miscellaneous. There were a variety of complications exhibited by isolated cases. One patient with a primary rib lesion developed an empyema, and another apparently died of asphyxia from massive local disease. One patient, with a primary Ewing's sarcoma of the sacrum, had a "spontaneous pneumothorax" believed to be due to extensive intrathoracic mestastases. One patient, with a primary femoral lesion, developed thrombophlebitis in the affected leg.

METASTASES

More consistently than is so with any other type of bone neoplasm, Ewing's sarcoma is apt to metastasize early and to produce wide dissemination of the disease. In 11 of this series of 91 cases there was no available information concerning the occurrence or location of metastases; all died of the disease and probably did have metastases that were unrecognized or were not apparent at the time of last examination. Six additional cases are either

alive and free of disease or have died of other causes without known metastases. The remaining 74 cases have been analyzed and provide information regarding the location and behavior of metastases.

Anatomic location. Since autopsies were performed in only 14 of the cases, the anatomical site of metastases herein tabulated is based on clinical, roentgenographic and only occasionally, on pathologic (biopsy and autopsy) examination (Table VI). In 47 cases the lungs were found to be involved by metastases, usually multiple and discrete. Next in order of frequency was

TABLE VI

Location of Metastases

(based on clinical findings in 74 cases of Ewing's sarcoma, dead or living with disease.)

Site		Cases
Lungs		47
Skull and scalp		32
Vertebrae		21
Bones of pelvis		20
Lymph nodes:		
Groin	9	
Axillary	4	
Supraclavicular and neck	3	16
Femur		14
Humerus		11
Orbit		9
Ribs		9
Pleura		8
Intracranial		6
Abdominal viscera		5
Tibia		4
Mandible		4
Skin and soft parts		4
Mediastinum		3
Scapula, clavicle, radius, sternum and fibula, one each		5

the skull and scalp which showed metastases in 32 cases. The bones of the pelvis were involved in 20 cases, the spinal column in 21, the femur in 14, and the humerus in 11 cases. Many other sites were occasionally involved by metastases as indicated in Table VI. It is obvious from this study that the next most common site for metastases, after the lungs, is the other bones of the skeleton, and that the lymph nodes and viscera were believed to be involved in only five instances.

As has already been stated the occurrence of neurological complications in Ewing's sarcoma is more frequent than chance alone would allow. The vertebrae were involved by metastases in 21 instances, and the intracranial region in 6, each of which might have induced neurological complications. The occurrence of metastasis to the bones or soft tissues of the orbit in nine cases is likewise noteworthy and one of us witnessed a case in which both eyeballs protruded from their sockets and ruptured before death.

The distribution of metastasis as determined at autopsy in 14 cases is shown in Table VII.

Characteristics of Metastases. On the basis of a study of 74 cases it may be said that, in general, metastases possess the same characteristics as the primary tumor. When superficially located they often present a palpable, firm, and possibly slightly tender tumor. Pain is frequently referable to the metastases. As has been suggested, the occurrence of fever in a patient that has had Ewing's sarcoma usually indicates metastases or local recurrence. The roentgenographic appearance of the metastases as well as the primary tumor is invariably one of osteolysis. Obviously the anatomical location of the metastasis chiefly determines its behavior; thus, chest metastases are often associated with cought, pulmonary suppuration, expectoration, and fever, but rarely hemoptysis. Metastases in the skull may be relatively painless while those in a vertebra may be extremely painful and associated with

TABLE VII

Location of Metastases

(based on autopsy findings in 14 cases of Ewing's sarcoma.)

Site	Cases
Lungs	9
Pleura	8
Mediastinum	6
Skull and scalp	5
Bones of pelvis	5
Ribs	5
Vertebrae	4
Femur	3
Dura	3
Humerus	3
Soft tissues	3
Tibia	2
Orbit	2
Retroperitoneal nodes	2
Liver	2
Pericardium	2
Fibula, brain, mandible, axillary nodes, diaphragm, spinal cord, one each	6

(Note: The peripheral bones and brain were not examined in all cases.)

radicular pain. The metastases of Ewing's sarcoma are apt to be progressively less radiosensitive as multiple areas make their appearance.

Treatment of Metastases. By the time metastasis has occurred in Ewing's sarcoma the chances of a cure are nil. For this reason probably, and because of the extreme radiosensitivity of these lesions, the treatment of metastases in this series has been practically confined to roentgen therapy. Of the 74 cases presenting metastases, no treatment was administered to the secondary lesions in 20 cases because the metastasis was relatively asymptomatic or because the patient was in the terminal stages of the disease. In the remaining 54 cases the following methods were employed: roentgen therapy in 42 cases, radium element pack in two cases, and both of these agents in eight cases. In the remaining two cases the metastases were treated with surgery; a thyroidectomy was performed in one under the misapprehension that a primary thyroid tumor existed, and in the other, a groin dissection was per-

formed at the time of hipjoint disarticulation for a Ewing's sarcoma of the tibia with metastasis to the groin nodes. The results obtained by all of these methods proved gratifying since in almost every instance the patient showed symptomatic improvement for a time and since there was frequent objective evidence of complete disappearance of the metastases. Whether the treatment of the metastases materially lengthened the patient's life cannot be determined, but it certainly appears to have rendered the remaining days more comfortable.

END RESULTS

Four patients in this series of 91 cases were lost to follow-up; all were living with disease at the time of their last examination. One other case, in which the autopsy was performed at Memorial Hospital, had but a meagre clinical record. These five must necessarily be considered as treatment failures but there is too little information available to include any one of them in an estimate of survival rates. Of the remaining 86 patients, 12 are living. One other patient (Case 3) lived for 14 years and 7 months and then died of an intercurrent episode of acute appendicitis with peritonitis but without evidence of a recurrent or metastatic tumor, so he must be regarded as a therapeutic success. The group of fatalities include 73 patients who have been followed to their death from Ewing's sarcoma.

Deaths. The time interval between the institution of definitive therapy and death in all 73 cases is known. The shortest interval occurred in a patient who succumbed to wide dissemination of the disease one week after admission to the hospital. The longest interval, 5 years and 7 months, was noted in a case treated with roentgen rays and thigh amputation. According to Chart II if the interval between treatment and death is analyzed by six-month periods it will be noted that more patients died during the second half-year following treatment than in any other half-year period. The average survival from the time of treatment to death in these 73 cases, however, was 18.7 months.

Autopsies were performed in 13 of the 73 cases, as well as in one other of the entire series of 91 patients (15.5 per cent). In all 14 cases a diagnosis of Ewing's sarcoma had been established by biopsy or had been seriously considered clinically. It is felt, therefore, that even where the protocols fail to mention it, a careful search was made in each instance to uncover unsuspected clinical evidence. No finding is recorded that is at variance with the clinical diagnosis of primary Ewing's sarcoma of bone. Other than the primary tumor and its metastases there were no constant autopsy findings recorded, except that the majority of patients appeared to have had bronchopneumonia, atalectasis, or pulmonary edema which, in these cases, was believed to be the immediate cause of death.

Living Patients. Twelve patients in this series are living. Seven of these are now alive with evidence of dissemination of disease which either is

under treatment or appears to be temporarily under control. Five patients are living and well without evidence of recurrence or metastasis.

Five-year survival. For the purpose of computation it is obvious that the twenty-five year period from 1918 through 1942 must be employed. Of the 73 patients who were first examined at Memorial Hospital during this period, only 3 lived without evidence of recurrent or metastatic disease for a period of five or more years following the institution of definitive therapy. Two of these patients are alive and well today 6½ years and 12 years following treatment. The third patient lived for 14½ years following treatment and then died of acute appendicitis with peritonitis but without evidence of a recurrent or metastatic tumor.

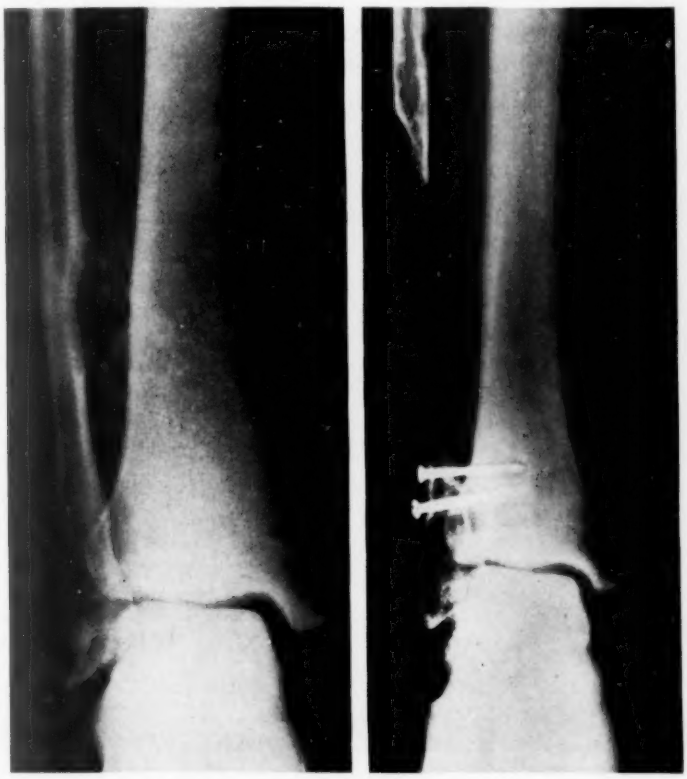


FIG. 7. (a.) (Case 1)—Atypical appearance of Ewing's sarcoma in lower end of left fibula. Ewing made the diagnosis on open biopsy. (b.) Roentgenogram 5 years after resection of tumor bearing segment of fibula with stabilization of the mortise by means of 2 vitallium screws which were subsequently removed.

CASE REPORTS

Case 1.—B. C., aged 22, was admitted to the Ruptured and Crippled Hospital on June 11, 1941, complaining of a "lump" just above the left ankle of 1½ years duration attributed by the patient to a kick. He complained of moderate pain in

this area ever since the injury. Prior to admission, an open biopsy had been performed elsewhere and 10 roentgen ray treatments had been administered. On June 12, 1941, resection of the lower end of the left fibula was performed with fixation of the remaining fragment to the tibia with screws (Fig. 7). A review of the slide of previous biopsy was reported as Ewing's sarcoma of bone. The pathologic examination of the surgical specimen showed no residual tumor present. The patient was discharged from the Ruptured and Crippled Hospital on June 30, 1941, and then referred to Memorial Hospital for further follow-up. The patient was then seen at frequent intervals and remained symptom free. On March 23, 1946, he was admitted to Memorial Hospital and 2 days later under local anesthesia, the vitallium screws were removed from the left lower leg. Since that time, the patient has remained symptom free with no functional loss. He was last seen and found to be free of disease on January 28, 1948, 6½ years after original treatment.

FIG. 8. (a.) (Case 2)—Ewing's sarcoma of upper right humerus confirmed by open biopsy. Treated with roentgen rays and Coley's toxin. (b.) Roentgenographic appearance 10 years later. Patient alive and well 12 years.

Case 2.—L. L., aged 13, was admitted to Memorial Hospital on April 14, 1936, stating that one year previously he noticed the onset of aching pain in the upper portion of his right arm. The pain increased in severity during the next two months so that the patient consulted a doctor who stated that he had a tumor. On July 4, 1935, at another hospital an open biopsy was performed which substantiated the diagnosis of tumor but temporarily relieved the patient of his pain. Because of the recurrence of pain the patient was referred to this institution. Physical examination revealed a firm nodular tumor underlying the previous biopsy scar which was nontender and which did not appreciably interfere with the function of the arm. A review of the biopsy sections was reported as showing endothelioma of bone. Following his open biopsy in July, 1935, the patient had been given 1870 r x 2 high

voltage therapy elsewhere. In this institution, the patient was given 1500 r x 3 high voltage roentgen ray treatment and was then admitted to the hospital for a course of Coley's toxin. He received a total of six intramuscular injections and was discharged improved. Although the patient was symptom free and showed no signs of recurrence of the tumor, in July of 1936 he was given further high voltage roentgen ray therapy in this institution for a total of 1000 r x 3 to the right upper humerus. As a result of these two courses of radiation therapy, it was estimated that the patient received doughly 6,025 r tissues dose in the tumor. The patient has since been followed in this clinic as well as by his local physician and has remained free of disease and shows only some atrophy in the region of the right shoulder presumably secondary to his roentgen ray therapy. The patient was last examined on November 18, 1947, and found to be in excellent health without evidence of recurrent disease 12 years since first treatment. (Fig. 8.)

FIG. 9 (Case 3)—Early roentgenogram. Clinical diagnosis of osteomyelitis. Biopsy interpreted as osteosarcoma and later revised to Ewing's sarcoma. Patient remained well 14 years and died of acute appendicitis with peritonitis.

Case 3.—H. S., aged 8, was struck in the leg with a sled while at play in January, 1920. Because of persistent pain in the right ankle, roentgenograms (Fig. 9) were made and the boy was taken to the Ruptured and Crippled Hospital where, in March, 1920, an incision and drainage of the right fibula was performed under the mistaken diagnosis of osteomyelitis. Because of persisting symptom of pain, the patient returned to the Ruptured and Crippled Hospital and a right mid thigh amputation was performed in June, 1920. Eight weeks later, a right groin dissection was performed because of grossly enlarged nodes. The patient was referred to Memorial Hospital on October 26, 1920, because of a firm mass deep in the iliac fossa above the area of groin dissection. A total of 10,109 mgs. hours was administered to the right groin with the radium element pack at 6 cm. distance, with improvement. The patient was discharged from Memorial Hospital on November 6, 1920, and referred back to

TABLE VIII

End Results in the Series of 73 Cases of Ewing's Sarcoma treated from 1918 through 1942.

Determinate Group—with histologic verification

Dead		70
Free of disease more than 5 years		3
Living and well	2	
Dead without disease after 5 years	1	
Total		73
Successful results		3
Five-Year Survival-rate		4.1%

the Ruptured and Crippled Hospital for the administration of Coley's toxin. Although at the time of admission, roentgenograms of the chest were reported as showing metastasis in the lungs, this finding was never confirmed on subsequent examinations. This patient was seen at infrequent intervals during the ensuing years and remained

symptom free without evidence of recurrence or metastasis. In January, 1935 14½ years later, the patient had an attack of acute appendicitis with generalized peritonitis to which disease he succumbed on January 31, 1935, without evidence of recurrence or metastasis from his original Ewing's sarcoma.

The five-year survival rate in this series of 73 cases (Table VIII) is 4.1 per cent, an extremely low survival rate, in fact somewhat lower than is commonly believed to apply in Ewing's sarcoma. It dramatically emphasizes our belief that Ewing's sarcoma is an extremely malignant lesion, one that is exceeded in poor prognosis only by leukemias.

SUMMARY

This report is based upon a study of 91 histologically proved cases of Ewing's sarcoma of which the end result after five or more years is known in 73 cases.

Attention is called to the predominance of the male sex, the preponderance of cases in the age-group from five to 25 years, and the simulation of an infectious or inflammatory process as evidenced by frequent febrile reaction, leukocytosis, and even by the roentgenographic appearance.

The difficulty sometimes encountered in distinguishing this disease from osteogenic sarcoma is also mentioned, with due emphasis being placed upon the importance of securing microscopic confirmation *prior* to treatment. As is pointed out, this is especially indicated because of the masking of the histologic picture following even small doses of roentgen therapy.

In young children Ewing's sarcoma may be exceedingly difficult to distinguish from metastatic neuroblastoma; in older children, adolescents and young adults, reticulum cell sarcoma of bone and angiosarcoma may also closely resemble it. The more favorable prognosis of reticulum cell sarcoma of bone and its response to doses of roentgen therapy, smaller than are required to inactivate permanently Ewing's sarcoma, makes its recognition a matter of importance.

The various methods of treatment of Ewing's sarcoma have yielded uniformly poor end results. This is amply demonstrated by the fact that only three out of 73 cases (4.1 per cent) survived five years or more. Regardless of the method employed, whether immediate surgery, preoperative irradiation, or irradiation alone or in combination with Coley's toxins, the ultimate result is practically always death from widespread metastases. Neurological complications are frequent and disturbing. No known method has as yet succeeded in overcoming the tendency of dissemination of the disease to the lungs, to other bones, and sometimes even to the lymph nodes and viscera. Ewing's sarcoma presents a challenge to the profession to devise a totally different mode of attack. In the meantime all that can be accomplished in the vast majority of cases is palliation for a period of from one to three or more years. Such palliation is usually best achieved by roentgen therapy.

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Discussion.—Dr. Norman L. Higinbotham, New York: In opening the discussion on Dr. Coley's paper I should like to emphasize some of the more important phases of this disease. The film on the screen represents one of the earliest lesions we were able to obtain, and I believe demonstrates very clearly the cortical origin of a purely osteolytic lesion. The process is just beginning to invade the medullary cavity and to set up a periosteal reaction. Formerly it was considered that this tumor was medullary in origin. After analyzing four cases similar to this one, we found that the tumor had a probable cortical rather than a medullary origin. The process goes on and eventually invades the entire cortex circumferentially.

This is a rather typical picture produced in the later stages of Ewing's sarcoma. There is diaphyseal involvement, a fusiform shape which is quite characteristic, complete osteolytic destruction of the cortex all the way around the bone, lamellation or so-called onionskin appearance of the petriosteum and, as the tumor has advanced, it has produced these radiating spicules outward from the bone. This sunburst appearance was originally described as pathognomonic for osteogenic sarcoma. However, in our experience we find that it occurs equally often in Ewing's sarcoma.

Another quite characteristic appearance produced by Ewing's sarcoma is this so-called moth-eaten appearance or cracked ice appearance. Here again is observed the diaphyseal involvement, the fusiform-shaped tumor extending upwards to the metaphyseal region and leading to imminence of pathologic fracture. When pathologic fracture occurs it may complicate the roentgenologic diagnosis.

This shows a 12-year-old boy with a diaphyseal lesion, purely osteolytic; even though there is a pathologic fracture one would suspect the diagnosis of Ewing's sarcoma which was confirmed by the microscope. Considerable difficulty in differential diagnosis may occur, however. Here is a picture which closely resembles, perhaps, fibrous dysplasia, and one might think also of reticulum cell sarcoma. This is the type of case in which biopsy is extremely important. In this case the pathologic report on the biopsy was malignant tumor, probably Ewing's sarcoma. This was later confirmed and low thigh amputation was carried out. The gross specimen shows the medullary cavity from which the tumor has been removed, also the complete cortical destruction and periosteal reaction which was quite evident on the roentgenogram.

The hazard of giving radiation therapy without a microscopic diagnosis is borne out by this particular case. In this young girl the clinical and roentgenographic diagnosis was Ewing's sarcoma. A course of radiation therapy was outlined for this lesion at the upper end of the femur and we proceeded with it. Then a biopsy was done and the pathologist reported that he could find only chronic osteitis. Accordingly, we felt that an error had been made in our clinical and roentgenographic judgment and further irradiation was withheld. However, a year and a half later this picture of an obviously malignant tumor was seen, and a second biopsy confirmed the diagnosis of Ewing's sarcoma. Had biopsy been done prior to irradiation therapy, as should have been done, we feel sure we would have had the correct diagnosis at the outset. The patient died of metastases six and a half months after this picture was taken.

Dr. Coley mentioned the three five-year survival cases, and I shall review them briefly. This 22-year-old boy had a lesion of the fibula, diagnosed by biopsy as Ewing's sarcoma. Preoperative irradiation was given to this area well above and well below the actual lesion. Then resection of the tumor-bearing section of bone was carried out and the mortise of the joint was stabilized with two vitallium screws. These were removed five and a half years later. The patient is living and well six and a half years following operation and was seen just a month ago.

The second patient is a 13-year-old boy with a lesion in the upper end of the humerus, diagnosed by biopsy as Ewing's sarcoma. A total tissue tumor dose of 6000 r units was estimated to have been given upon completion of irradiation therapy. In conjunction with and following this therapy he was given a long series of injections of Coley's toxin. He was last seen in December, 1947, alive and well 13 years after the original therapy.

The third and last case is an 8 year old boy with a lesion in the lower end of the fibula diagnosed as Ewing's sarcoma by biopsy. High amputation was done and Coley's toxin was given postoperatively. This patient survived 14 years, only to die of acute appendicitis with petritonitis, although entirely free of malignant disease.

Three cases surviving a period of five years are hardly enough from which to draw any conclusions as to treatment. One might legitimately ask what is the treatment for this rather hopeless condition. It is our impression at the present time that, given a diagnosis of Ewing's sarcoma, planned treatment should include biopsy to prove the nature of the lesion, preoperative irradiation, removal of the tumor either by resection or by amputation above the bone involved, and postoperative administration of Coly's toxin.

Dr. J. J. Morton, Rochester, N. Y.: When George Peck asked me to write on treatment of this disease, there were some known facts; namely, that it is a disease of youth, that males predominate, that a great many of the lesions are below the waistline, that fever is a frequent accompaniment, and that osteomyelitis is a frequently mistaken diagnosis. Many have come to me who have been operated on for osteomyelitis; they have shown no growth of any organism, the osteomyelitis, so-called, does not improve, and the doctor begins to suspect that he is dealing with something else, and it is usually Ewing's tumor.

Since 1940 there have been two or three series reported, but none so extensive as this one from the Memorial. Dr. Myerding reported a series from the Mayo Clinic and Dr. Campbell reported a series from Memphis. The Bone Sarcoma Registry also put out a report in the forties. Those are the only series reported and, for that reason, I think this is a very important paper.

The pathology is quite confusing, although I think it is a definite entity. We have been told in the past that adrenal sympathetic tumors resemble it very closely but can be differentiated by the fact that they form rosettes. Recently, some Ewing's

tumors have been shown to form rosettes of tissue. If you stain cells for reticulum, you will find that Ewing's tumor forms reticulum also. Recently Dr. Stout told me that he was very hesitant about making a diagnosis of Ewing's tumor; that, in fact, he did not know how to do so; and he is a trained pathologist. The surgeon, therefore, has a good deal of difficulty in deciding what he is really dealing with. Nevertheless, I think Ewing's sarcoma is a true tumor because we have had enough postmorten examinations to know that the adrenals are not involved and that this is not a lymphosarcoma. The Australians will not admit that there is such a tumor, and it is in doubt in some of the Scandinavian countries—so it is still controversial.

As to treatment, at the time I was asked to write on the subject treatment was the same as for any form of malignancy, except that the Memorial had a tremendous amount of radiation which was used on patients with this diagnosis. Dr. Ewing pushed it to the extreme, but he admitted to me that he was trying to find the best dosage to use. If you review all the literature you will find, I am sure that there are 18 or 20 patients that have gone beyond the five-year period, some considerably beyond. Treatment has been quite varied; some by surgery, some by radiation in various ways, some by a combination of agents and some by x-ray alone. There are two or three cases which have been healed by x-ray alone for a period of several years. Meyerding agrees that irradiation treatment holds the premier position, multiple cross-fire ports being used.

I agree with Dr. Coley that this is a most discouraging disease, and I hope we will find some better method of treatment.

FURTHER EXPERIENCES WITH PERITONEAL IRRIGATION FOR ACUTE RENAL FAILURE

Including a Description of Modifications in Method

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With the assistance of Drs. Edward D. Frank, Leon A. Manheimer, Felix Heimberg, Alexander M. Rutenburg, Henry H. Banks, Marvin M. Nachlas

FROM THE KIRSTEIN LABORATORY FOR SURGICAL RESEARCH, BETH ISRAEL HOSPITAL, AND THE DEPARTMENT OF SURGERY, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

In our last communication on this subject[1], reported in this journal in November, 1946, we stated that the method of peritoneal irrigation as then developed was still in an experimental stage owing to certain inherent limitations: the formula of the irrigating fluid did not correct acidosis or hypocalcemia; the absorption of water from the irrigating fluid was not under adequate control; some protein and probably water-soluble vitamins were lost into the irrigating fluid; and most significant of all, peritonitis could not be prevented.

In this report, which is based on a clinical experience of some 14 additional patients in renal failure, we present modifications in the method which we have introduced as the lessons of our experience indicated. Analysis of the clinical data which follows demonstrates that a satisfactory degree of fluid and electrolyte balance can be achieved and recovery of renal function facilitated. The danger of peritonitis, which has been greatly minimized but by no means obviated, still constitutes the chief hazard of the technic. Even so, the results now obtainable[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] are such as to warrant continued exploitation of this method for treating acute renal failure, providing recovery of renal function is still possible.

MODIFICATIONS IN METHOD

A. *The irrigating fluid* has been altered so that it now contains the following amounts of anhydrous substances in grams per liter: NaCl 7.4, KCl 0.2, $CaCl_2$ 0.2, $NaHCO_3$ 1.0, dextrose 10.0; plus gelatin* 10.0 and $MgCl_2.6H_2O$ 0.22.

The reasons for these changes are: (1) the NaCl is reduced to 0.74 per cent because some patients develop hyperchloremia. An even greater re-

** The work described in this paper was done under a contract, recommended by the Committee on Medical Research of the Office of Naval Research of the United States Navy and Harvard University.

† Read before the Meeting of the American Surgical Association, May 27-29, 1948, Quebec, Canada.

duction in chloride with a corresponding substitution of sodium lactate might be desirable, but the resulting greater alkalinity might prove too irritating to the peritoneum and would require an adjustment of the pH after autoclaving and cooling. The difficulty of carrying out a sterile titration procedure on large fluid volumes has deterred us from carrying out this modification. Partial substitution of NaCl by $NaHCO_3$, which would have the advantage of better counteracting the acidosis, would also make the fluid too alkaline.

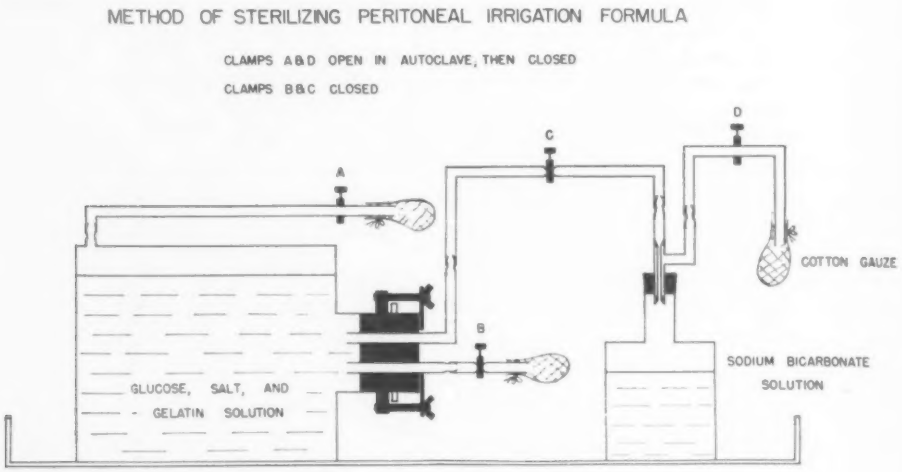

Fig. 1.

(2). The calcium ions have been doubled because the blood levels of calcium are regularly low in uremic patients and because the ionic calcium concentration requirement is higher when phosphate is elevated. Even with the increase in calcium ions, intravenous calcium therapy is still necessary. A further increase in calcium ion concentration of the irrigating solution may be worthwhile and will be tested.

(3). The phosphate is omitted because the blood phosphate concentration is excessive in uremia and because calcium and magnesium are precipitated from the irrigating solution by phosphate if their concentration or the pH is in excess of that in unmodified Tyrode's solution.

(4). To avoid absorption of water the solution is made more hypertonic by adding gelatin to a concentration of 1 per cent and by increasing the glucose from 1.5 Gm. to 10 Gm. per liter. The increase in hypertonicity might be obtained by a sufficient amount of either gelatin or glucose alone. Glucose alone in sufficient amount is possibly too irritating. The advantage of some glucose in higher concentration than we have used heretofore is

* We are grateful to the Atlantic Gelatin Company for this material.

Fig. 2.

Fig. 2.

COMPLETION OF PERITONEAL IRRIGATION FORMULA

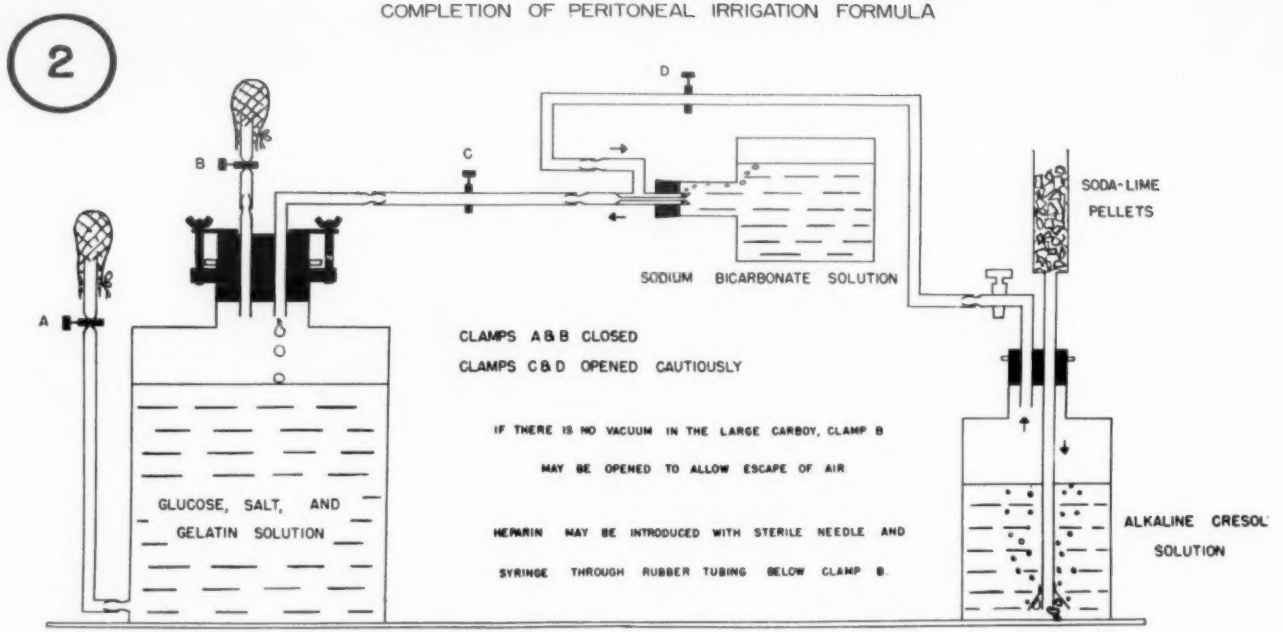

Fig. 3.

that it supplements the limited amount that can be given intravenously to supply the basal caloric requirement.**

B. *Preparation of the Irrigating Fluid* (Figs. 1 and 2). In order to avoid contamination of the fluid after sterilization, the sodium bicarbonate, which must be autoclaved apart from the remainder of the solution, is added after cooling, by arranging the flasks in tandem during autoclaving (Fig. 1), so that the vacuum created during cooling accomplishes transfer of the bicarbonate solution to the carboy on opening the appropriate stopcocks (Fig. 2). All tubing is clamped during the cooling period. Air entering the system after cooling is bubbled through an alkaline solution of parachlorphenol and cresol. In several tests, cultures from cotton plugs filtering the air which

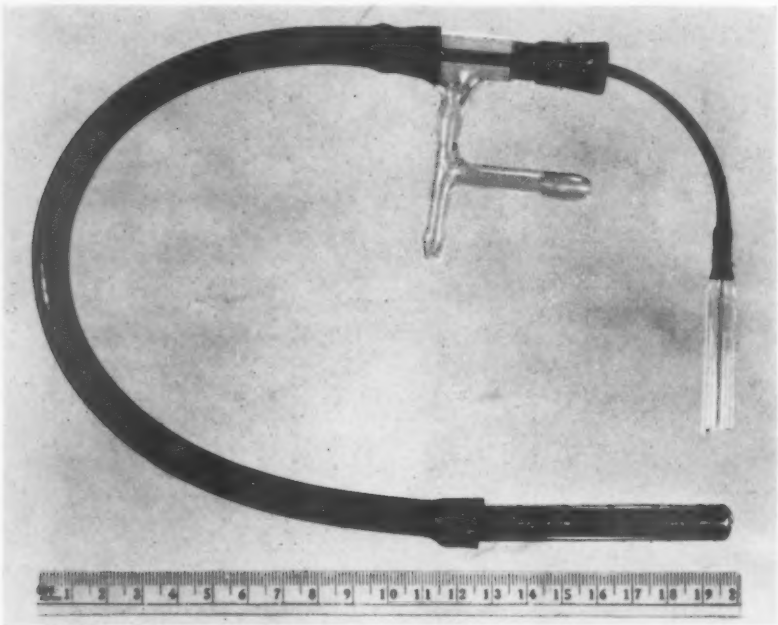

Fig. 4.—Illustrating structure and design of the flexible sump drain.

had passed through the cresol filter were found to be sterile. Cultures from samples taken at the point of entrance of the final irrigation formula into the abdominal wall are also uniformly sterile. Because the bacterial filter, formerly interpolated at this point, impedes the flow of fluid containing gelatin it no longer is used and is unnecessary since the solution is sterilized by autoclaving in the containers and connecting apparatus from which it is delivered to the patient. Heparin and penicillin, formerly added to the solution after sterilization, are now omitted.

** Some 200 Gm. of glucose are absorbed in 24 hours from the irrigating fluid and the remainder (150-200 Gm) is given in a 15 per cent concentration intravenously.

C. *Irrigation Procedure.* To prevent the absorption of water it is essential that the irrigating fluid shall not be allowed to lose its hypertonicity. Recovery of the fluid before equilibration can occur is accomplished by confining the fluid to the pelvis and by the use of a flexible-shaft sump drain the three-inch stainless steel tip of which is placed in the depth of the cul-de-sac. Continuous irrigation from a separate inflow tube to the sump or intermittent filling and emptying by using the sump as a two-way system is used.

The sump drain is placed as follows: Under spinal anesthesia a short transverse incision down to the deep fascia is made beneath the costal margin. Through a short incision opposite the anterior superior spine the peritoneal cavity is opened. A subcutaneous tunnel connecting the two incisions is made. The metal end of the flexible sump drain (Figs. 3 and 4) is inserted through the upper incision and passed along the subcutaneous tunnel to the lower incision, through which it enters the peritoneal cavity, where it is placed under direct vision into the bottom of the cul-de-sac (Fig. 5). The peritoneum, fascia, and rectus muscle are closed snugly around the rubber portion of the sump drain. The skin of the lower incision is closed over the tube and the skin of the upper incision is closed around the tube, which, at this level, projects through the sterile dressing. Then it is attached to glass connecting tubes (Fig. 5), one of which connects to the fluid carboy, another to a suction line and a third to an air inlet. The suction line leads to a fluid collecting carboy and a negative pressure regulator. The air delivered to the sump drain is passed in fine bubbles through the sterilizing solution (alkaline parachlorphenol and cresol).

The system is operated by a series of screw clamps shown in Figure 5. About a liter of fluid is allowed to enter the pelvic cavity through clamp C, while clamps A and B are opened, and all the fluid is withdrawn into the collecting bottle on the floor at the bedside. Fresh fluid is introduced and the cycle repeated. The procedure is carried out by a nurse, who must be in constant attendance.

Samples are taken by needle aspiration daily from the sterilized outflow tube at A for study of the drainage fluid for the presence of bacteria or leucocytes. Samples taken daily from the inflow tube at C have always been sterile. Chemical analysis is done on aliquots taken from the collecting bottle.

The patient lies semi-erect, so that the fluid in the pelvis remains below the upper incision. Thus no contact by possible ebb and flow can be made between the fluid and the skin of the abdominal wall. Fig. 6, a bedside photograph, shows gastro-intestinal drainage, intravenous therapy and peritoneal irrigation proceeding simultaneously. The patient is also on constant bladder drainage, so that urine studies together with blood analyses permit accurate assessment of renal function.

Irrigation is discontinued after 72 hours, or sooner if diuresis begins. If the drainage fluid shows bacteria or more than a few leucocytes per high

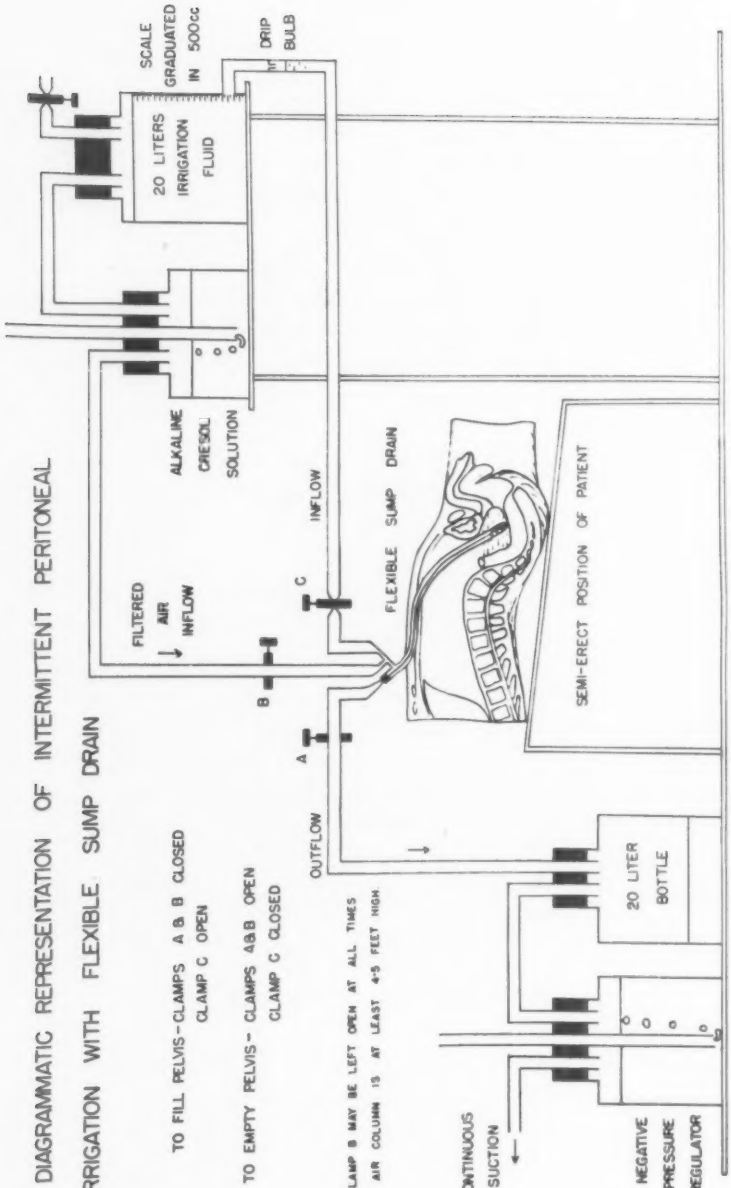
DIAGRAMMATIC REPRESENTATION OF INTERMITTENT PERITONEAL IRRIGATION WITH FLEXIBLE SUMP DRAIN
TO FILL PELVIS - CLAMPS A & B CLOSED
CLAMP C OPEN
TO EMPTY PELVIS - CLAMPS A & B OPEN
CLAMP C CLOSED
CLAMP B MAY BE LEFT OPEN AT ALL TIMES IF AIR COLUMN IS AT LEAST 4-5 FEET HIGH
SCALE GRADUATED IN 500cc
DRIP BULB
20 LITERS IRRIGATION FLUID
ALKALINE CRESOL SOLUTION
FILTERED AIR INFLOW
INFLOW
OUTFLOW
A
B
C
FLEXIBLE SUMP DRAIN
SEMI-ERECT POSITION OF PATIENT
20 LITER BOTTLE
CONTINUOUS SUCTION
NEGATIVE PRESSURE REGULATOR

Fig. 5.

power field, peritoneal contamination may be presumed to be present and the procedure is terminated at once. Even if the drainage fluid remains sterile the irrigation is stopped after seventy-two hours. This we judge from experience is the maximum period of continuous irrigation that is compatible with the avoidance of frank peritonitis. Should diuresis fail to occur thereafter, the procedure can be reinstituted upon the return of high levels of retention products or the disappearance of peritoneal irritation if present.

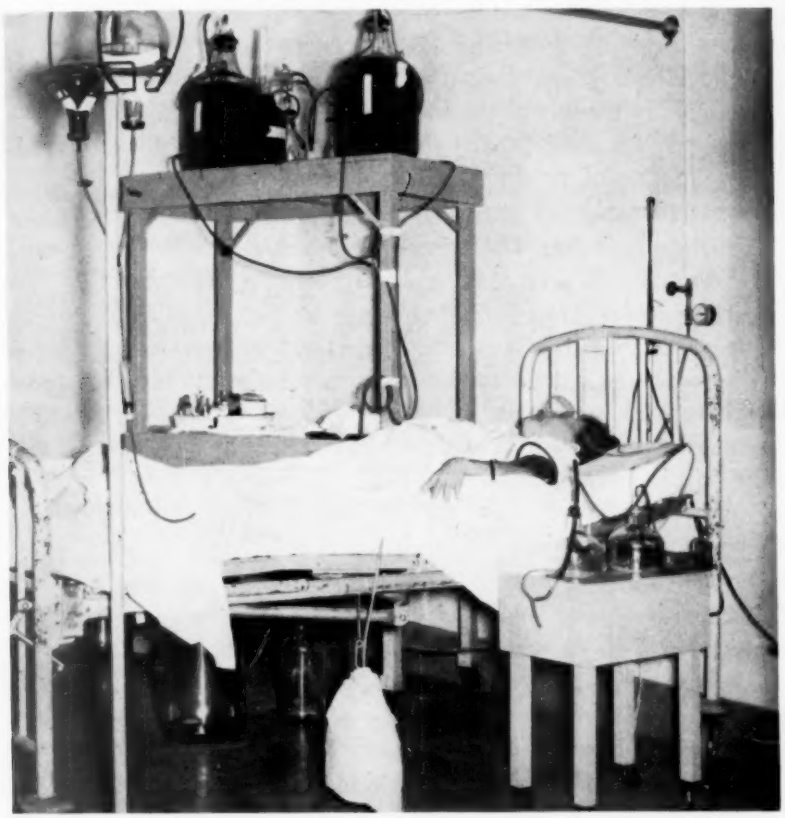

Fig. 6.—Showing gastro-intestinal drainage, intravenous therapy and peritoneal irrigation proceeding simultaneously.

Distorted gastrointestinal function (anorexia, vomiting, ileus, distention) is nearly always present in uremia, so that the patient must be intubated and all alimentation given parenterally.

Not a few patients are unwisely overhydrated beforehand, burdened with edema, particularly of the lungs, which are abnormally vulnerable in uremia. In order to prevent overhydration of the patient, it is necessary to limit the parenteral fluid administered daily to 1000 cc. This imposes a severe limitation on the amount of glucose which the patient can be given. Moreover, this fluid is also needed to administer the sodium lactate necessary to treat the acidosis ordinarily present. In some patients loss of fluid by continuous

gastro-intestinal aspiration can be considerable and may prove helpful in removing water or in preventing overhydration.

Some uremic patients are disoriented. Paraldehyde or barbiturates may be needed to control extreme restlessness.

If diuresis sets in, it begins by a small, but sharp, increase in volume output. The next day the output doubles or triples and the following day this volume may be doubled so that within a few days the output reaches a normal volume or commonly a polyuria is reached. For some days the urine is pale, with a low specific gravity and a urea concentration that is about equal to that of the blood. Since irrigation will have been discontinued, the blood urea or NPN; in the meantime, will rise from the reduced level produced by the irrigation. As renal function recovers, the urea output rises and finally overtakes the rate of production, so that the blood concentration curve returns toward normal.

Efficient peritoneal irrigation abstracts some 25-50 Gm. of urea daily. This is more than the normal urea production of a starving patient. As soon as the urinary urea output reaches some 10 Gm. per day in the recovery phase after acute renal failure, it can be safely assumed that the renal function will keep pace with urea production and the outlook for recovery is good. Phenolsulfonphthalein excretion and urea clearance tests at this time will show low function (20-30 per cent of normal) and the specific gravity of the urine will be between 1007 and 1010. The ileus will have largely disappeared and oral alimentation will be near normal except for occasional nausea or food intolerance. Vitamins and antibiotics will be discontinued as improvement occurs, but blood may be needed for persistent anemia.

All of the foregoing details of therapy have been applied to each patient only in the last four cases, except that one was irrigated for only 48 hours. Three of these developed peritoneal contamination, two with *E. coli* and one with *B. subtilis*. Three of the four patients survived; the fourth died of an irreversible renal injury. It appears, therefore, that even preventing contamination from the skin, air, or irrigating fluid by careful observance of all the details described, will not prevent peritonitis.

E. coli has been the usual pathogen responsible for peritonitis. It is possible that in the uremic patient serosal irritation by the irrigating fluid may cause transmural migration of intestinal bacteria.* Therefore, the routine oral administration of sulfthalidine in maximal doses is used to diminish the intestinal content of *E. coli*. Penicillin is given intravenously to all patients from the outset. Streptomycin is used only after infection occurs, because of rapid development of fastness. These antibiotics did not prevent or cure *E. coli* peritonitis, even when they were also added to the irrigating fluid. Polymyxin or duomycin, when available, may prove more useful for this purpose.

The cases which follow are presented in detail for the purpose of deline-

ating the way in which the method, as previously published, was altered as a result of experience from one case to the next, until it evolved into the form now being employed.

CASE REPORTS

Case 5*.—W.S. (BIH 88032): A 43-year-old man, who had been in good health, cleaned furniture with carbon tetrachloride for two hours in a warm, closed room, a week before admission. He felt "groggy" and then developed throat irritation, cough, fever, costovertebral angle and right upper quadrant pain and tenderness, subconjunctival hemorrhages, nosebleeds, occipital headache, diarrhea, increasing dyspnea, icterus and oliguria. During the three days before admission to this hospital he received 10,000 cc. of fluid and produced a total urine output of 390 cc. Generalized and pulmonary edema developed.

On admission he was acutely ill, dyspneic, vomiting, icteric, and complaining of diffuse abdominal pain. He showed orbital and conjunctival hemorrhages, an enlarged liver, and abdominal muscle spasm. Arterial pressure was 180/100 mm. Hg. The urine contained albumin and had a maximal specific gravity of 1010. The blood NPN was 105 mgm. per cent, CO_2 combining capacity 47.5 vols. per cent, calcium 7.4 mg. per cent, phosphate 10.3 mg. per cent and the icteric index 32.5. Treatment for three days with concentrated glucose solution given intravenously, oxygen and penicillin was attended by steady deterioration of the patient's condition, with increasing dyspnea, tachycardia and daily urine outputs of 65 cc., 135 cc. and 300 cc. respectively. The NPN rose to 135 mg. per cent. The BUN was 76 mg. per cent. On the fourth hospital day, an inflow tube and sump drain were inserted into the peritoneal cavity under local anesthesia and irrigation was started.

The irrigating solution contained glucose in 1½ per cent concentration in addition to the salts of Tyrode's solution. Peritoneal irrigation was carried out for 48 hours at a flow rate of 35 cc./min. during the first day and of 25 cc./min. during the second. The urea N concentration of the outflow fluid was 42-45 mg. per cent. The total urea removed on the first day was 46 Gm. and on the second 35 Gm. The peritoneal urea clearance rate averaged 21-22 cc./min. The blood NPN after 48 hours of irrigation was lowered to 94 mgm. per cent and the blood urea N to 44 mg. per cent. The CO_2 combining capacity, however, dropped to 29 vols. per cent and the blood phosphate remained elevated at 11 mg. per cent. During the two days of irrigation the urine volumes were 215 cc. and 225 cc. respectively. The urine urea content was only 75 to 80 mg. per cent and the total *urinary* urea excretion during the 48 hours of irrigation was 0.8 Gm.

There was a deficit of outflow ranging from 3 to 7 liters per 24 hours, which, in part, represented leakage into dressings and in part may have been due to absorption of fluid. Increasingly severe pulmonary edema and dyspnea did not respond to medication, which included oxygen, tourniquets, morphine, alkali therapy and calcium. The patient died on the sixth hospital day.

Postmortem examination* disclosed severe pulmonary edema and confluent bronchopneumonia. The kidneys and liver were edematous and congested. There was no evidence of peritoneal infection. Microscopy showed a lower nephron nephrosis, i.e., normal glomeruli, necrobiosis and desquamation of the ascending limbs of Henle's loops and distal convoluted segments, especially at the cortico-medullary junction, where interstitial edema, lymphocytes and plasma cells were present.

* See reference[1] for cases 1-4.

Comment. Acute renal failure was due to carbon tetrachloride nephrosis[13, 14]. The peritoneal irrigation progressed with ease and efficiency, but acidosis, hyperphosphatemia and hypocalcemia were not corrected. Peritoneal infection did not occur. Pulmonary edema and confluent bronchopneumonia were the immediate cause of death. The carbon tetrachloride fumes undoubtedly produced some of the pulmonary pathology, but excessive fluid administration prior to hospital admission and the absorption of irrigating fluid from the peritoneal cavity were major contributing factors in the development of pulmonary edema.

The increase in glucose from 1.5 Gm. to 15 Gm. per liter of irrigating fluid did not prevent water absorption.

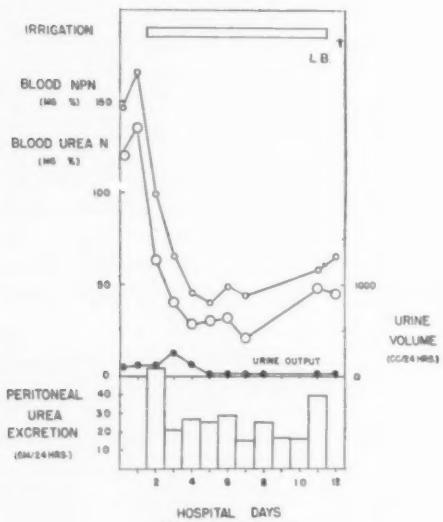

Fig. 7. Case 6.

Case 6.—L. B. (BIH 88238): A 55-year-old man, with rheumatic heart disease and subacute bacterial endocardities, entered another hospital for progressive oliguria. Study there showed albumin and many red and white cells in the urine, no concentration of diodrast by the kidney and a blood NPN of 140 mg. per cent. Physical examination disclosed malnutrition, rheumatic heart disease and a blood pressure of 95/50 mm. Hg. Repeated blood cultures yielded streptococcus viridans. Three thousand cc. of 5 per cent glucose in distilled water, administered intravenously, daily for five days failed to induce diuresis. Edema of the face and legs developed and the patient became drowsy. Renal failure was believed to be due to acute glomerulonephritis. He was transferred to us for irrigation.

During the first 36 hours prior to irrigation he received 100,000 units of penicillin intramuscularly, every two hours, and 1500 cc. of 30 per cent dextrose intravenously. The daily urine output did not exceed 100 cc. The blood NPN rose to 166 mg. per cent, the BUN to 136.5 mg. per cent, the blood pressure to 150/100 mm. Hg. The CO_2 combining capacity was 37 vols. per cent, the blood NaCl 534 mg. per cent, calcium 7.1 mg. per cent, phosphate 11.0 mg. per cent, serum protein 6.73 Gm. per cent (albumin 2.37 Gm. and globulin 4.36 Gm. per cent). The patient became semi-comatose. Temperature and pulse rate were normal.

Continuous irrigation by an inflow tube and sump drain was started. *Tyrode's solution containing 2 per cent glucose* was used at a rate of 35 cc. per min. The blood NPN and urea N levels returned to normal by the third day of irrigation (Fig. 7, Table I.). Concomitantly the patient became alert. A brief bout of pulmonary edema following the intravenous administration of a liter of 30 per cent glucose on the second day of irrigation was treated by tourniquets and digitalization. Some 450 Gm. of glucose was absorbed daily from the peritoneal cavity.

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*We are indebted to the Department of Pathology under the direction of *Dr. Monroe Schlesinger* for the reports of the postmortem findings.

TABLE I—*Case 6*

Day	Adm.	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th
Peritoneal fluid:													
Urea N (mg. %)	..	57.5	19.5	24.3	22.0	23.0	17.0	24.2	..	37.5	33.8	41.8	..
Urea clearance (cc./min.)	..	..	28.0	18.0	34.0	27.0	17.0	..	..	..	..	27.0	..
Culture	..	..	..	..	..	..	..	*E. coli* *G + diplococci*	..	..	*B. pyocyaneus* *B. subtilis*		..
Urine:													
Urea N (mg. %)	260	250	107.5	0	0	12.5	7.5	35.0	0	..	..	32.5	15.0
Specific gravity	..	1.006	1.006	1.005	1.006	1.006	1.010	1.010	..	..	..	..	..
Reaction	..	alk.	alk.	acid	acid	alk.	acid	acid	..	..	..	..	..
Albumin	..	4+	4+	4+	4+	3+	..	3+	..	..	..	..	..
Blood:													
CO_2 cap. (vol. %)	37.0	37.0	26.0	25.5	22.5	26.0	41.5	40.0	..	..	..	..	36.0
Cl^- (as NaCl mg. %)	534	..	630	..	780	..	790	776	..	..	..	..	776
PO_4^{--} (mg. %)	11.0	..	..	..	..	..	6.5	5.6	..	..	..	..	6.5
Ca^{++} (mg. %)	7.1	..	..	..	8.0	..	..	..	..	..	..	..	..
Plasma protein (Gm. %)	6.7	..	..	..	7.4	..	..	..	..	..	..	..	..
Aterial Blood Pressure (mm. Hg)	100/50	130/80	150/100	150/100	130/60	130/70	130/80	110/70	100/70	110/60	120/60	..	..
Intravenous fluid:													
30% glucose in H_2O (cc.)	..	1000	1021	1000	1000	..	..	..	1000	1000	1500	1000	..
Blood (cc.)	..	..	..	..	500	..	..	..	500	..	..	500	..

Acidosis increased, the CO_2 combining capacity having dropped to 22 vols. per cent by the fourth day of irrigation. The irrigating fluid, therefore, was modified by adding 2.35 *Gm. of sodium lactate per liter,* which raised the pH of the solution to 8.3. The blood CO_2 combining capacity returned to 41 vols. per cent within two days. This more alkaline solution was used thereafter in two of every three carboys of irrigating fluid. Penicillin was continued and blood and plasma given from time to time. The patient remained afebrile. He was able to eat on the fifth day of irrigation, but oliguria persisted.

On the seventh day of irrigation, culture of the peritoneal outflow fluid disclosed *E. coli* and gram positive diplococci. Thereafter, a third of a gram of streptomycin was added to each 20 liter carboy of solution and irrigation was continued. The general condition remained good for another two days, after which abdominal pain and tenderness, productive cough, fever, and a rapid pulse appeared. The patient died on the tenth day of irrigation. Blood chemical findings just before death were near the normal range. Peritoneal culture the day before death disclosed *B. pyocyaneus* and *B. subtilis.*

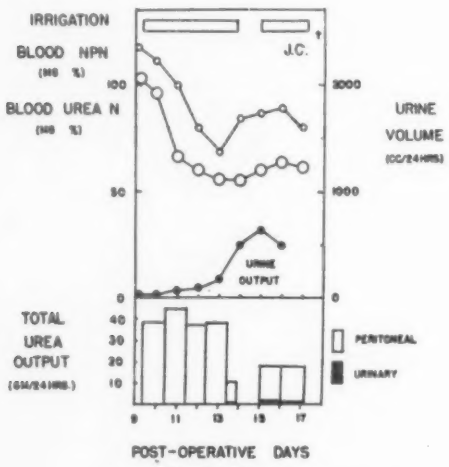

Fig. 8. Case 7.

Autopsy showed mitral stenosis and insufficiency, subacute bacterial endocarditis of the mitral valve, pulmonary edema, basilar atelectasis and early diffuse fibrinopurulent peritonitis. The kidneys were swollen and congested. Microscopically they showed widespread fibrosis, epithelial proliferation, focal necrosis, and polymorphonuclear leucocytic infiltration of the glomeruli, i.e., chronic glomerulonephritis with an acute exacerbation.

Comment. The patient was a dubious choice for this therapy. Since the endocarditis might be expected to respond to penicillin, it was considered desirable to treat the renal failure by continuous irrigation, ten days of which produced marked clinical improvement and restoration of the blood chemistry to near normal levels. While systemic edema, present on admission, did not increase, the bout of acute pulmonary edema following 30% glucose intravenously may have played some role in the patient's death. The addition of sodium lactate to the irrigating fluid corrected acidosis, so that intravenous alkali therapy was unnecessary. Diffuse fibrinopurulent peritonitis developed and was the immediate cause of death. The degree of renal damage suggests that spontaneous recovery from uremia was unlikely.

Case 7.—J.C. (BH88742): A 56-year-old man, underwent a one-stage Whipple operation for carcinoma of the ampulla of Vater and common bile duct nine days before transfer to this hospital. The patient's condition remained good for the first five postoperative days, during which time he was able to eat and walk. He then developed fever, jaundice, distention, progressive oliguria and a rising BUN. He was transferred to us on the 9th postoperative day for irrigation. On inserting the inflow tube and sump drain into the peritoneal cavity, a large volume of clear, icteric peri-

toneal fluid was found and evacuated. Culture of the fluid, reported later, disclosed alpha streptococci and diphtheroids. *The irrigating fluid was Tyrode's solution plus 2 per cent glucose, penicillin and streptomycin. From time to time, one third of the chloride in the solution was replaced by bicarbonate or lactate to combat acidosis.* In the first three days the irrigation flow rate was 36 cc. per minute, but thereafter recurrent interference with outflow substantially reduced the average rate of flow. The blood NPN and urea N levels were substantially reduced and the blood CO_2 combining capacity increased to 36-48 vols. per cent, but the blood calcium remained low (see Table II and Fig. 8). After five days of irrigation, an increase in urine output from practically none to 500 cc. per day occurred.

TABLE II—*Case 7*

Postoperative Day	9th	10th	11th	12th	13th	14th	15th	16th	17th
Peritoneal Fluid:									
Urea (mg. %)	..	35	41	33	38	37	..	30	37
Urea Clearance (cc./min.)	..	13	19	19	22	8	..	9	11
Culture (streptococci) (diphtheroids)			E.coli						
Urine:									
Urea N. (mg. %)	..	33	..	120	158	143	133	165	168
Sp. gravity	..	1.008	1.010	1.016	1.011	1.010	..	..	..
Reaction	..	alk	alk	alk	alk	alk	..	..	..
Albumin	..	2+	0	4+	4+	4+	..	..	..
Blood:									
CO_2 cap. (vol %)	41	45	36	47	48	43	..	48	50
Cl^- (as NaCl mg. %)	..	584	..	680	700	696	..	646	..
PO_4^{---} (mg. %)	..	5.5	..	4.5	..	..	..	5.7	..
Ca^{++} (mg. %)	..	7.4	..	7.4	..	..	..	6.7	..
Plasma protein (Gm. %)	..	6.6	..	..	6.3	..	..	..	7.8
Hemoglobin (%)	75	68	65	64	70	..	..	..	..
Arterial B.P. (mm. Hg)	130/70	140/80	140/80	140/80	140/70	130/70	140/70	120/70	90/70

The clinical condition—fever, tachycardia, jaundice, hallucinations, and delirium—worsened. A large quantity of cloudy fluid containing pancreatic amylase oozed from the operative incision for several days. Intestinal distention necessitated intubation, which yielded 2000-4000 cc. of fluid per day. Penicillin (1-2 million units) and streptomycin (2-4 Gm.) were given intramuscularly daily and transfusions for anemia were given repeatedly. Streptococci were not found again in the peritoneal fluid, but *E. coli* appeared in the outflow fluid on the third day of irrigation.

A comparison of outflow with inflow volumes indicated no significant retention of irrigating fluid and no generalized edema developed. But pulmonary edema appeared abruptly on the eighteenth postoperative day, when the patient died.

Postmortem examination disclosed confluent bronchopneumonia, marked peripancreatic fat necrosis and hemorrhage, multilocular purulent peritonitis and obstruction at the biliary anastomosis. The histologic examination of the kidneys disclosed little damage. A mild degree of focal "lower nephron" nephrosis, in the healing stage, was found.

Comment. Renal failure consequent to the development of peritonitis is a familiar experience. The existence of peritonitis was not realized when

the irrigation was started, but became obvious later. Irrigation was continued in order to observe its effectiveness in the circumstances. The blood nitrogenous levels responded in spite of recurrent blocking of outflow, which was possibly due to the peritonitis. It is difficult to assess the influence of the

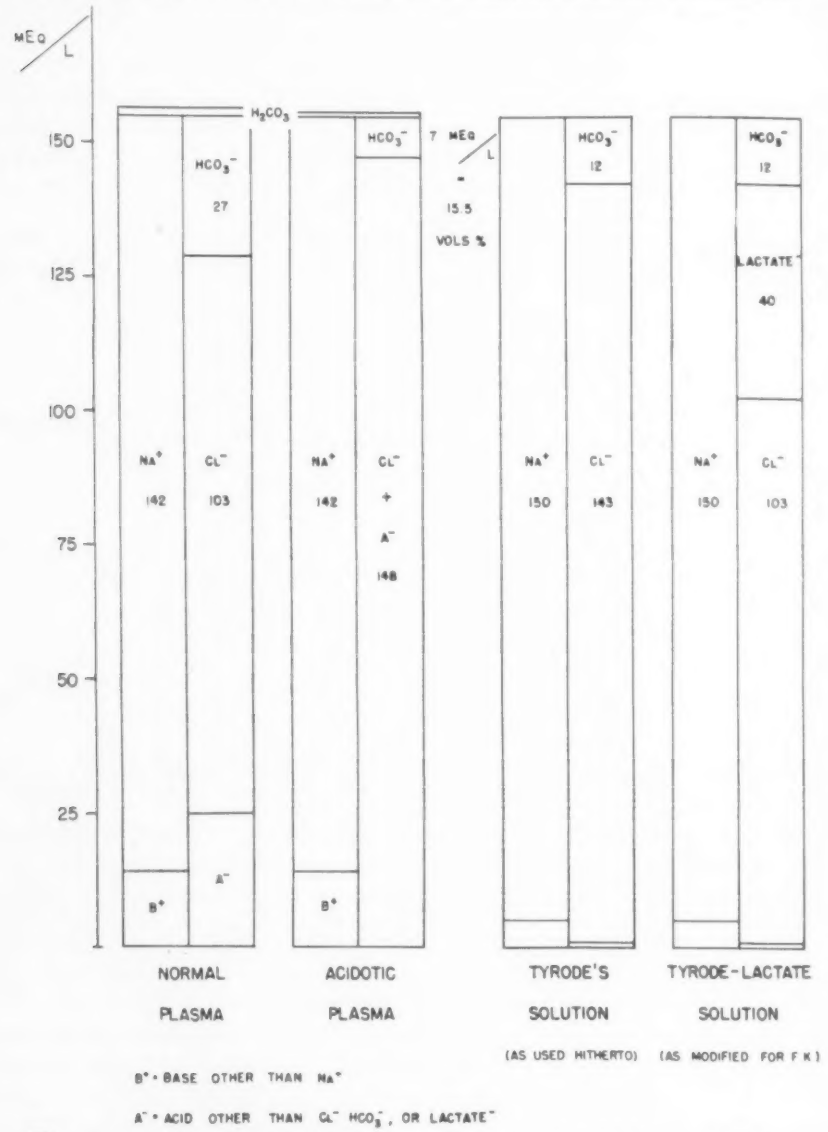

Fig. 9. — Diagram (modeled after Gamble) of acid-base equivalence of modified irrigating solution used in case 8.

irrigation procedure on the course or spread of the peritonitis. On the basis of our experience with irrigation after peritonitis has set in, we are inclined to believe that it may have done more harm than good.

In this patient, as in the last, edema did not occur. The substitution of

bicarbonate or lactate for one-third of the ionic equivalent of chloride in the irrigating solution resulted in effective control of acidosis.

Case 8.—F.K. (BIH 91435): A 44-year-old chronic alcoholic, was admitted to another hospital complaining of progressive reduction in urinary output of three weeks' duration, associated with a dull, persistent ache in both flanks and mid-back. One week before admission he stopped working because of anorexia and extreme fatigability. He was then able to void only a few cc. of bloody urine daily and noticed puffiness of the eyelids. On admission the lower eyelids were ecchymotic, the liver edge was three finger breadths below the right costal margin, the blood pressure was 145/85 mm. Hg., the red cell count 3.7 million and the hemoglobin 12 Gm. per cent. The urine was alkaline and contained albumin, glucose, red and white cells. Cystoscopy and retrograde pyelography revealed no abnormality. The blood NPN levels were 138, 165, and 150 mg. per cent, the CO_2 combining capacity 32, 29, and 24 vols. per cent respectively, on three succeeding days after admission. Bilateral renal decapsulation was done the day following admission. No gross abnormality of either kidney was noted. During this three-day period the patient voided a total of 110 cc. of urine and received a total of 13 liters of fluid.

On transfer to us for peritoneal irrigation the patient was drowsy, and respiration was acidotic. There were moist rales at the right lung base, but no peripheral edema. Both flank incisions were healing well. The blood pressure was 145/80 mm. Hg. The blood NPN was 124 mg. per cent, BUN 109 mg. per cent, CO_2 combining capacity 25.5 vols. per cent and chlorides 458 mg. per cent. No urine could be obtained. Five hundred cc. of 30 per cent glucose in water were given intravenously for starvation acidosis.

On the following day, continuous peritoneal lavage, through an inflow tube and sump drain was instituted. A modified Tyrode's solution* containing 2 per cent glucose was used (Fig. 9).

The pH of this solution after autoclaving was 7.9.

Because of incipient pulmonary edema, no fluid was given intravenously at first. The irrigating fluid was relied upon to provide glucose. Penicillin, streptomycin, and the water-soluble vitamins were given intramuscularly. Irrigation was continued at flow rates averaging 31, 36, 38, 23, 23, and 26 cc. per minute on the six successive days respectively (see Table 3 and Fig. 10). During the first three days the patient showed progressive subjective and objective improvement. In this period the peritoneal urea clearance varied from 8.5 to 15.6 cc. per minute, and the blood NPN and BUN fell to 68 and 45 mg. per cent respectively. The blood CO_2 combining power dropped steadily to 15.5 vols. per cent in spite of sodium lactate in the irrigating fluid, and the absorption of some 250 Gm. of glucose per day. Five-hundred cc. of one-sixth or one-third molar solution of sodium lactate, therefore, was given intravenously each day and the blood CO_2 combining capacity returned to normal. The daily urine output, which was never greater than 150 cc., eventually declined toward zero. The daily blood pressure varied from 150 to 170 mm. Hg. systolic and 80 to 100 mm. Hg. diastolic.

	Gm. per liter
NaCl	5.7
$NaHCO_3$	1.0
Na lactate	4.5
KCL	0.2
$CaCl_2$	0.1
NaH_2PO_4	0.05
$MgCl_2.6H_2O$	0.22
Dextrose	20.0

*Composition of modified Tyrode's solution

Mild abdominal distention was not relieved by tube suction. Thereafter, peritoneal lavage became progressively less efficient and the blood NPN and urea N levels slowly increased. On the eighth day local signs of peritonitis appeared. The outflow fluid contained many polymorphonuclear leucocytes and gram negative bacilli, including *E. coli, B. aerogenes* and Friedlander's bacillus. He expired that evening.

Postmortem examination disclosed diffuse fibrino-purulent peritonitis. The kidneys were large and the perirenal fat was edematous, indurated and hemorrhagic. Most of the true renal capsule had been removed. Microscopic examination disclosed a tubular nephritis. The great majority of the tubules showed swelling, disintegration, necrobiosis, and desquamation in the proximal and distal convoluted portions and in the limbs of Henle's loops, with evidence of early regeneration, particularly in the proximal convoluted tubules. There was considerable interstitial edema.

TABLE III—*Case 8*

Hospital day	Adm.	1st	2nd	3rd	4th	5th	6th
Peritoneal fluid:							
Urea N (mg. %)	..	47	19	12	13	12	15
Urea clearance (cc. min.)	..	16	12	9	4	5	6
Culture	..	..	..	..	..	*E. coli* Friedlander's bacillus *B. aerogenes*	..
Urine:							
Urea N (mg. %)	..	38	86	112	107	198	..
Urea clearance (cc. min.)	.....	.....	.....	negligible	.....	.....	.....
Specific gravity	..	1010	1002	1007	1008	..	..
Reaction	..	alk.	alk.	acid	acid	..	..
Albumin	..	4+	3+	2+	3+	..	..
Blood:							
CO_2 cap. (vol. %)	26	21	16	23	36	..	48
Cl^- (as NaCl mg. %)	458	564	..	..	..	..	530
Fluid balance:							
Peritoneal inflow (L.)	..	47	52.5	55.2	36	33.5	38
Peritoneal outflow (L.)	..	43	52	53	26	36	40
Lactate (cc.)	..	500(M/6)	500(M/3)	500(M/6)	..	..	..
Oral	..	2190	1505	1510	2000	1700	800
Gastric drainage (cc.)	..	..	..	100	1500	1200	900
Glucose retained from irrigating fluid (Gm. /day)	..	206	182	185	109	309	250

Comment. The cause of the loss of renal function was not known. Autopsy showed acute diffuse tubular damage. Although histologic evidence of early regeneration was seen, there was no recovery of renal function and no evidence that decapsulation had produced benefit.

For some 48 hours the irrigation accomplished its purpose, except for failure to control acidosis in spite of the presence of lactate in the irrigating solution. The acidosis was readily corrected by intravenous sodium lactate. Edema did not develop. The treatment failed and the patient died because of peritonitis due to gram negative bacilli. The efficiency of irrigation decreased after the first two days, possibly because of peritonitis, which probably developed two days before it was recognized clinically.

Although sodium lactate in the irrigating solution was effective for control of acidosis in two of the three patients in whom it was used, all three developed peritonitis. This may have been due to the prolonged period of irrigation, but the possibility that the increased alkalinity of the solution may have irritated the peritoneum sufficiently to reduce its resistance to bacterial growth or to encourage migration of bacteria through the wall of the intestine, led us to abandon the use of sodium lactate in the solution.

The formula for subsequent clinical use then determined upon was modified Tyrode's solution with gelatin and glucose for the purpose of preventing fluid absorption. It was felt that further increase in glucose alone for this purpose, might prove too irritating. Because the gravity flow of the solution containing gelatine through the diatomaceous bacterial filter is too slow, the filter thenceforth was removed from the inflow circuit.

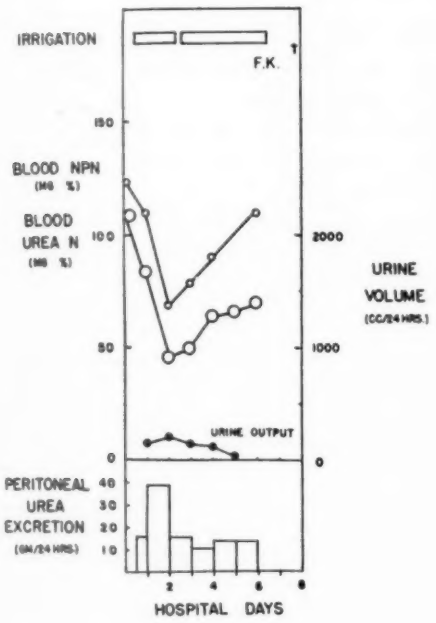

Fig. 10. Case 8.

Case 9.—G.H. (BIH 91590): A 53-year-old man underwent perineal prostatectomy at another hospital. After 48 hours of normal urine output, acute renal failure set in following a severe reaction to the intravenous infusion of 200 cc. of 5% glucose in saline. The febrile reaction was followed by wound hemorrhage and shock. Acidosis was prevented by the intravenous administration of sodium bicarbonate. Severe oliguria persisted for 10 days. The patient was then sent to us for peritoneal irrigation. He was in advanced uremia, with edema from overhydration. *Peritoneal irrigation was carried out with a modified Tyrode's solution containing 1 per cent gelatin and 2 per cent glucose.* The patient died 31 hours after irrigation was started. During this time 18.5 Gm. of urea in the 43 liters of outflow fluid was recovered. The outflow fluid remained sterile. Postmortem examination disclosed intestinal distention, but no peritoneal infection. The kidneys showed a typical lower nephron nephrosis, with healing in progress.

Comment. The etiology of the kidney injury is obscure. A pyrogenic and apparently hemolytic reaction accompanied the intravenous administration of glucose in saline and was followed by a prolonged period of hemorrhagic shock. No incompatible blood was given. There was no recovery of renal function in spite of the histologic evidence of healing.

Peritoneal irrigation was initiated when the patient was moribund. Little benefit could have been expected and none was observed. The presence of gelatin (1 per cent) and glucose (2 per cent) was effective in preventing the

absorption of water from the peritoneum. Outflow equalled inflow volume, and the patient's edema did not increase. No peritoneal infection occurred.

Case 10.—E.M. (BIH 91718): A 43-year-old male, was admitted to a neighboring hospital complaining of bilateral low-back pain of eight weeks' duration, progressive oliguria of three weeks' duration, and anorexia, nausea and vomiting for four days. One week prior to entry he experienced a severe chill. On admission, the blood pressure was 140/90 and the pulse 68. There were moist rales at both lung bases, but no other positive physical findings. Laboratory data were normal except for a blood NPN of 187 mg. per cent, a CO_2 of 36 vols. per cent. No urine was found on catheterization of the bladder. Retrograde pyelography revealed no abnormality of bladder, ureters or renal pelves. High spinal anesthesia failed to induce urinary flow. He was transferred to us for peritoneal irrigation.

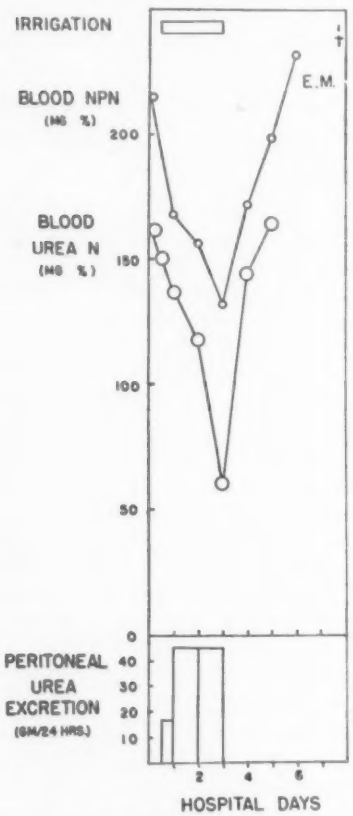

Fig. 11. Case 10.

There were fine moist rales in the lower lung fields. The abdomen was distended and typanitis. The right Babinski sign was positive, there was bilateral ankle clonus and involuntary muscle twitchings. Vomiting was frequent. The blood pressure was 150/85 mm. Hg. Laboratory data showed a RBC 3,870,000; Hgb. 13.6 Gm.; WBC 19,500; NPN 216 mg. per cent; BUN 164 mg. per cent; CO_2 combining power 46.5 per cent. There was no urine.

Three hours following admission *continuous irrigation through an inflow tube and sump drain was started, using a modified Tyrode's solution** flowing at an average rate of 24 cc. per minute for two and one-half days. Water-soluble vitamins and penicillin were given intramuscularly and sulfathalidine orally. On the second day of irrigation the patient was given 150 grams of glucose intravenously in a total of 1700 cc. of water. The chest x-ray film showed pulmonary congestion and bilateral hydrothorax.

The blood urea clearance by peritoneal irrigation varied from 12.3 to 19.0 cc. per minute during this period and the urea excretion averaged 40 grams per day. The blood NPN and urea N declined, but the CO_2 combining power remain essentially unchanged (Fig. 11 and Table 4).

	Gm. per liter
gelatin	10.0
glucose	5.0
$NaHC_3O$	2.25
NaCl	6.25
KCl	0.2
$CaCl_2$ (anhyd)	0.1
$MgCl_2.6H_2O$	0.2
NaH_2PO_4	0.05

*Composition of irrigating solution:

Substantial subjective improvement was evident, but the daily urine output remained less than 30 cc. Sixty hours after irrigation was started the peritoneal drainage fluid was cloudy and yielded a growth of staphylococcus albus and diphtheroids, which were also cultured from the wounds the next day. Irrigation was immediately discontinued.

Thereafter, the blood NPN and the clinical evidence of uremia increased. Abdominal distention required intubation. A peritoneal tap two days and again four days after cessation of irrigation, yielded a pure culture of *E. coli.* Streptomycin therapy was given (6 gm. in 48 hours) but the patient grew rapidly worse, developed mild generalized and pulmonary edema, became comatose and died four days after irrigation was discontinued. There was no urine output in the last 4 days of life.

Postmortem examination revealed yellow, cloudy peritoneal fluid and small flakes of purulent material covering the serosal surfaces of the upper abdominal viscera. There was mild edema of the lower lobes of the lungs. Both kidneys were markedly enlarged, swollen and deeply congested, weighing 260 Gm. each. Microscopy showed

TABLE IV—*Case 10*

Hospital day	Adm.	1st	2nd	3rd	4th	5th	6th	7th
Peritoneal fluid:								
Urea N (mg. %)	62.7	99.7	72.6	..	..	..	..	..
Urea clearance (cc./ min.)	12.3	19.0	12.7	..	..	..	..	..
Culture		sterile		*staph. albus* diphtheroids		*E. coli*		*E. coli*
Urine:								
Urea N (mg. %)	..	232	..	..	..	..	..	..
Reaction	..	alk.	..	..	..	..	..	..
Albumin	..	4+	..	..	..	..	..	..
Culture	..	*E. coli*	..	..	..	..	..	..
Blood:								
CO_2 cap. (vol. %)	46.5	38.5	38.5	40.5	42.0	29.0	51.0	..
Cl^- (as NaCl mg. %)	..	..	560	..	..	..	..	..
Plasma protein (Gm. %)	..	..	..	..	5.8	..	..	..
Hemoglobin (%)	..	76	94	100	..	..	..	..
Arterial Blood Pressure (mm. Hg)	150/85	130/75	120/80	130/90	120/60	105/60	..	..

crescentic epithelial proliferation, adhesions, splitting, thickening and fusion of the capillary basement membrane, or complete fibrosis of the great majority of the glomeruli. In many, necrosis, hemorrhage and an exudate of polymorphonuclear leucocytes were present. There was a diffuse interstitial infiltration of lymphocytes and plasma cells. No vascular lesions were found. Diagnosis: Chronic proliferative and acute exudative glomerulonephritis.

Comment. Although a presumptive diagnosis of glomerulonephritis was made on admission, the uncertainty of the diagnosis and, therefore, the possibility of recovery of kidney function led to a trial of peritoneal irrigation, which achieved a blood urea clearance of 12-19 cc/min., reducing blood nitrogenous levels, eliminating 40-50 grams of urea per day, and producing subjective improvement. One per cent gelatin and one-half per cent dextrose were used in the irrigating fluid. The outflow fluid volume was 0.6 to 6.0 liters less than the inflow per 24 hours.

Although on one occasion the peritoneal outflow fluid contained the same organisms found in the wound (staphylococcus albus and diphtheroids), the organism responsible for the peritonitis was E. coli, in pure culture. Streptomycin therapy produced no detectable benefit.

Changes in technic were then designed to exclude as rigidly as possible the introduction of bacteria *via* the irrigating fluid, even though the repeated finding of *E. coli* as the predominant infecting organism suggested that transmural migration of intestinal organisms was the likely source of the peritonitis: (1) The open-top sump drain was redesigned. A closed top to

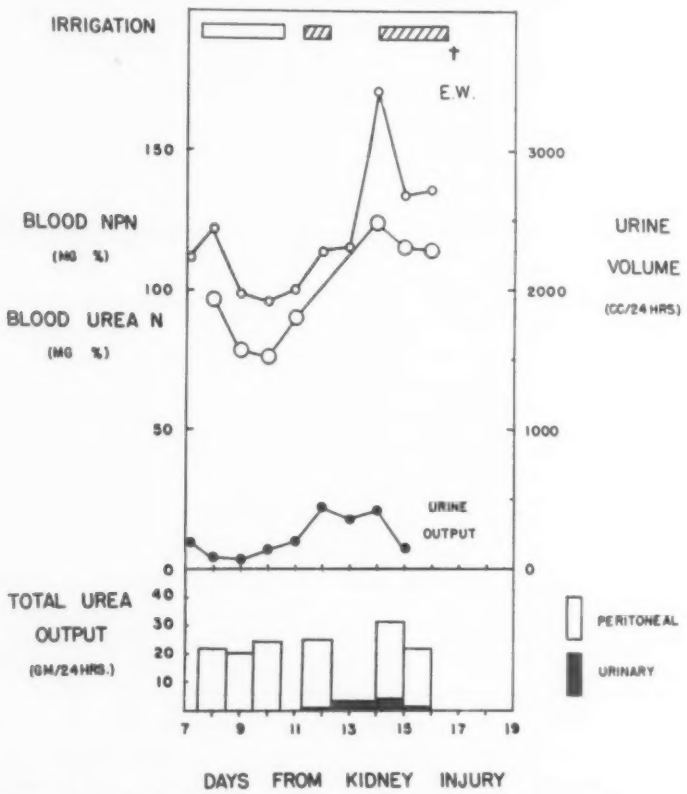

Fig. 12. Case 11.—(Open bar indicates continuous irrigation; cross-hatched bar indicates intermittent irrigation.)

prevent the escape of fluid into the dressings and a side-arm for the inlet of filtered air was provided.* (2) Another change in technic introduced at this time was the preparation of the irrigating fluid by adding all its constituents at once to cooled freshly distilled water and sterilizing by Berkefeld filtration rather than by heat. This was tried in the following case, but was later aban-

* The principle of a sump drain is to maintain atmospheric pressure in the sump cylinder so as to avoid drawing surrounding tissues into the drain. Structures were not drawn into the holes of the outside cylinder in spite of the slight negative pressure.

doned because of the lack of proper apparatus to filter safely large volumes of fluid under pressure. The technic now in use for preparing the solution was then devised and is described in the preceding section of this paper.

Case 11.—E.W. (BIH 92825): A 32-year-old woman, who had received sulfadiazine for pneumonia four years earlier, was given 0.5 Gm. of sulfdadiazine every four hours for three days for pain and swelling of the left cheek, associated with a slight sore throat. At the end of this period she noticed edema of the face and eyes, moderate pain and tenderness in the midback and inability to void more than very small amounts of urine. A catheter specimen of urine contained albumin (4+), many granular casts and red and white blood cells. The blood pressure was 130/90 mm. Hg. and the blood NPN was 122 mg. per cent. Catheterization of the ureters revealed no obstruction. During the subsequent four days treatment consisted in forced fluids, hypertonic dextrose, magnesium sulfate, penicillin intravenously and diathermy to the renal area. The urine output averaged 100 cc. per day. Edema increased; abdominal distention and cerebral depression appeared. She was transferred to this hospital for peritoneal irrigation after seven days of oliguria.

On admission the patient was drowsy; her color was ashen gray, with moderate cyanosis of the lips and finger tips. There was edema of the face, ankles and lower back. There was dullness to percussion over the right lung base posteriorly. The abdomen was distended with fluid. A definite Chvostek sign was elicited.

A stainless steel inflow tube and a closed-top outflow sump (Fig. 3) were inserted into the peritoneal cavity. *Continuous irrigations was started with a modified Tyrode's solution (Solution I*) containing 1 per cent glucose, one-half per cent gelatin, heparin and penicillin.*

Streptomycin for *E. coli* urinary infection, water-soluble vitamins, and penicillin were given parenterally. Several whole blood transfusions and a daily slow intravenous drip of 30 per cent glucose in 500 cc. of water were given. The stomach was intubated and calcium gluconate, concentrated glucose and sodium lactate were introduced through this tube. The tube could not be made to pass beyond the pylorus.

After three days of continuous irrigation with an average of 28 liters of fluid daily, and with the extraction of 20 Gm. of urea per day, there was definite clinical improvement (Fig. 12 and Table V). The patient became alert, well-oriented, and active. The daily urine volume did not exceed 200 cc. Edema decreased markedly. But increasing abdominal distention, fever and tachycardia led to discontinuing the irrigation. It was resumed 18 hours later. Phosphate was omitted from the solution (Solution II — see above), which was now introduced and withdrawn intermittently. A liter of fluid was allowed to dialyze for 45 minutes and then was removed by suction.

	*Solution I (sterilized by Berkefeld filtration)	Solution II (sterilized by autoclaving)
	Gm. per liter	*Gm. per liter*
NaCl	7.25	7.25
KCl	0.2	0.2
$CaCl_2$(anhyd.)	0.1	0.1
$MgCl_2.6H_2O$	0.2	0.2
NaH_2PO_4	0.05	0
$NaHCO_3$	1.5	1.5
Dextrose	10.0	10.0
Gelatin	5.0	5.0
Final pH 7.45		Final pH 8.1 — 8.5

TABLE V—*Case 11*

Day (from kidney injury)	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th
Peritoneal fluid:										
Urea N (mg. %)	36.3	30.4	42.9	56.5	..	..	..	89.1	85.8	85.8
Urea clearance (cc./min.)	8.0	8.4	10.3	6.8	..	..	..	5.7	11.0	11.0
Culture		sterile				sterile				*E. coli*
Urine:										
Urea N (mg. %)	71	207	194	310	280	372	507	429	528	..
Specific gravity	..	1.010	1.021	1.011	1.010	..	1.012	..	1.013	..
Reaction	alk.	alk.	acid	acid	acid	..	acid	..	acid	..
Albumin	4+	4+	4+	4+	4+	..	4+	..	3+	..
Cells	WBC RBC	WBC RBC	WBC RBC	WBC RBC	WBC RBC	..	WBC RBC	..	WBC RBC	..
Culture	*B. pyocyaneus* *E. coli*	*E. coli*		*B. pyocyaneus*			*B. pyocyaneus*			*B. pyocyaneus*
Blood:										
CO_2 cap. (vol. %)	..	35.0	53.0	44.5	38.5	..	57.0	54.0	38.5	58.5
Cl^- (as NaCl mg. %)	458	..	558	580	544	..	..	600	..	..
PO_4^{--} (mg. %)	..	11.4	..	10.7	10.0	..	..	8.9	..	..
Ca^{++} (mg. %)	..	6.9	..	7.4	7.7	..	..	6.9	..	..
Plasma protein (Gm. %)	4.9	5.6	..	5.2	5.2	..	.	5.1	..	..
Arterial Blood Pressure (mm. Hg)	..	120/60	120/60	170/110	150/90	..	..	150/100	120/70	..
Fluid exchange:										
Peritoneal inflow (L.)	37.0	31.7	28.0	25.2	..	..	..	17.5	7.2	7.2
Peritoneal outflow (L.)	29.0	32.7	24.0	23.0	..	..	..	15.0	6.5	6.5
Blood transfusion (cc.)	..	..	..	500	..	..	500	500	..	500

The abdomen became so severely distended by the sixth hospital day that the fluid introduced produced marked respiratory distress. Irrigation was discontinued and the tubes were removed. All measures for relief of distention failed. The patient became manic and disoriented. An enterostomy tube was placed in a loop of small bowel. Peritoneal fluid taken for culture during this procedure was sterile. The next day (eighth hospital day) stupor, dyspnea, techycardia and a blood NPN of 172 mg. per cent made it seem that, although urine output was increasing, adequate renal function would not occur soon enough to prevent death. A sump drain was re-inserted in the left lower abdomen under local anesthesia and intermittent irrigation was instituted, using the sump for both inflow and outflow. For some 30 hours there was progressive improvement in clinical and laboratory findings. The patient again became alert and co-operative. But *E. coli* was found in pure culture in the outflow fluid during the next two days. Acute pulmonary edema developed on the ninth hospital day. It subsided, but coma and decline in urine output developed and death followed in the tenth hospital day, 17 days after the original renal shutdown.

Postmortem examination revealed cerebral edema, congestion of the middle and lower lobes of the right lung and fibrinopurulent pelvic peritonitis. The kidneys were swollen and congested. Renal microscopy showed a lower nephron nephrosis, i.e., normal glomeruli, necrosis and hemorrhage of the lower tubular segments, which contained spherulo-radiate crystals, refractile to polarized light and resembling sulfonamide crystals. An interstitial exudate, most pronounced at the cortico-medullary junction, contained lymphocytes and plasma cells.

Comment. The apparent cause of the renal shutdown in this instance was sulfonamide hypersensitivity, produced by prior administration. The blood urea clearance achieved by peritoneal irrigation was not great enough to produce a substantial decline in blood NPN or urea N concentrations, but a large amount of urea was removed. Improvement in the uremic state resulted. Since this patient came to us considerably overhydrated, intravenous therapy for starvation acidosis and hypocalcemia was avoided. Intestinal distention was probably aggravated by the hypertonic glucose fed *via* the stomach tube. It is doubtful whether the enterostomy, though ill-advised, was responsible for the peritonitis, since the inflammatory reaction was confined to the pelvis and the enterostomy area was free of infection.

After this experience it was decided that the low blood calcium and the high blood phosphate should be treated not only by omitting phosphate but by increasing calcium in the irrigating fluid.

It was also decided at this time that the rigid sump drain was unsatisfactory, (1) because it was still possible for fluid to pass back and forth from the peritoneal cavity to the skin along the *outside* of the drain cylinder, and (2) because the tip of the drain could not be kept at the bottom of the pelvic cul-de-sac, which is necessary if a stagnant puddle which permits absorption of water and facilitates infection from contaminating organisms, is to be avoided. Consequently, the sump drain was shortened so as to form an aspirating tip to a flexible tube, which would be passed through the abdominal wall at staggered levels and would emerge from the abdomen well above the intraperitoneal fluid level, there to be attached to a closed system for inter-

mittent or continuous irrigation with the assurance of complete aspiration of the fluid, and without the possibility of ebb and flow between the skin and the peritoneal cavity.

Case 12.—E.P. (BIH 93042): A 36-year-old housewife (blood group O) received 500 cc. of incompatible blood (group A) after operation for a right tubal pregnancy at another hospital. During the transfusion a chill was followed by shock. Further transfusions (correctly matched) were given. Urine output decreased from 120 cc. on the first post-operative day to 0 cc. on the fifth, with progressive daily increase in blood NPN, which reached 140 mg. per cent on the fifth post-operative day, when she was transferred to this hospital.

On admission the patient was cyanotic, drowsy and responded only by feeble head movements. Respiration was rapid and shallow. There was dullness, bronchial breathing and a few crepitant rales at the right lung base posteriorly. The abdomen was diffusely distended, tympanitic and silent. There was a vertical suprapublic wound with skin clips *in situ*, draining blood and showing hemorrhagic extravasation. There was pitting edema of the lower back, thighs and ankles. Both optic disc margins were slightly blurred. The blood urea N was 138 mg. per cent, sodium chloride 492 mg. per cent, CO_2 combining capacity 55 vols. per cent, icteric index 13, calcium 5.7 mg. per cent, phosphate 9.0 mg. per cent and total protein 6.0 Gm. per cent. The Chvostek and Trousseau signs were negative.

A Miller-Abbott tube was passed beyond the pylorus, oxygen was given by mask and the intramuscular administration of penicillin and water-soluble vitamins was started.

The following morning the patient's color was better and abdominal distention was less. The chest signs were unchanged. In view of the duration and severity of the uremic state it was considered necessary to institute peritoneal irrigation without further delay. *Because of the condition of the incision and the inflammatory reaction of the peritoneum, intermittent filling and emptying of the peritoneal cavity was attempted through a large bore needle,* which was withdrawn after each filling and emptying. Approximately 2000 cc. of solution*, an arbitrary amount determined by the patient's tolerance, was introduced at each filling, allowed to remain for three hours, after which aspiration was undertaken. Multiple punctures in a variety of sites were required to withdraw the fluid, and only 1400 cc. and 1350 cc. of fluid respectively were recovered after the first two instillations. During this period the patient received a very slow (six-hour) intravenous infusion of 30 per cent glucose in 500 cc. of water. Soon after the third peritoneal filling (1500 cc.) the patient suddenly became deeply cyanotic and markedly dyspneic, with associated tachycardia, restlessness and apprehension. Chest signs, confirmed by x-ray, were consistent with massive pulmonary edema. Paracentesis did not remove a significant amount of fluid and the operative wound had now separated widely, down to the deep fascia. Because of the patient's extremely precarious condition, therapy was limited to snug taping of the lower abdomen.

	Gm.
NaCl	7.4
KCl	0.2
$CaCl_2$	0.2
$MgCl_2.6H_2O$	0.22
$NaHCO_3$	1.0
dextrose	5.0
gelatin	10.0
pH 7.1 (after autoclaving)	

*Composition of irrigating solution (per liter)

Pulmonary edema was treated by oxygen under positive pressure, morphine and a sharply upright position of the patient in bed. The following morning respiration was slightly less labored and was improved by a right thoracentesis, yielding 500 cc. of clear yellow fluid. Diffuse coarse pulmonary rales persisted. The abdomen was softer, apparently due to absorption of retained peritoneal fluid.

The fluid retained in the peritoneal cavity, as shown by the deficit in the fluid withdrawn, totaled 2750 cc. in the 7 hour period of intermittent irrigation. The peritoneal fluid removed had a urea concentration equal to that of the blood, so that in all 3.8 Gm. of urea were removed (blood urea clearance 8.0 cc. per minute). No improvement in blood nitrogen levels was accomplished and the CO_2 combining capacity dropped to 43 vols. per cent.

For a day and a half following the episode of pulmonary edema no fluid was given except for the oral administration of 160 cc. of normal sodium lactate. During this period the patient's color improved, respiration became less labored and the lung fields became clearer, though scattered moist rales and dullness at both bases persisted. Peripheral edema increased. Fever (103.8°) at the end of this period was attributed to pulmonary infection. Intramuscular streptomycin (4 Gm. daily) was started and penicillin was increased to 250,000 units every four hours.

By the afternoon of this, the eighth postoperative day, the patient showed signs of marked uremic intoxication. She was semi-comatose. There were frequent tetanic movements of the extremities. The blood NPN was 182 mg. per cent, urea N 163 mg. per cent and the CO_2 combining capacity 37.5 vols. per cent.

Intermittent irrigation with the single flexible sump drain was started. Five hundred cc. of solution was introduced, allowed to equilibrate for 15 minutes, then removed by gentle suction, and replaced by fresh solution. The entire cycle required approximately thirty minutes. The overall flow rate averaged 21 cc. per minute. After seven hours of irrigation the patient regained consciousness and recognized people in the room. The irrigation was continued for forty-four hours, during which the inflow volume totaled 57 liters and the outflow 56 liters. In the first 26-hour period the urea N content of the outflow fluid was 95 mg. per cent (blood urea clearance, 12 cc. per minute) and 61 Gm. of urea were removed. The blood NPN fell to 160 mg. per cent, but the CO_2 combining capacity dropped to 25 vols. per cent and the venous blood pH was found to be 7.1. Sodium lactate (250 cc. of N/6 solution) and 500 cc. of blood were given intravenously. The subcutaneous edema increased but the lungs were now entirely clear. In the next eighteen hours, the urea N concentration in the outflow fluid was 54 mg. per cent (blood urea clearance 8.2 cc. per minute) and 26 Gm. of urea were removed.

The clinical state deteriorated. In spite of the rapid administration of 1500 cc. of whole blood and 1,000 cc. of plasma and the slow infusion of 20 per cent glucose, the patient died in shock and coma on the tenth postoperative day, when the blood NPN was 152 mg. per cent and CO_2 combining capacity 40 vols. per cent. The peritoneal outflow fluid remained sterile throughout the period of irrigation. The urine output never exceeded 60 cc. daily.

Postmortem examination revealed no evidence of peritoneal irritation, except for a small fibrinous exudate on a loop of small bowel in the vicinity of the sump drain. The lungs were edematous. This probably developed terminally as a result of the large amount of fluid given in the effort to combat shock. The brain, too, was slightly edematous. The kidneys were slightly swollen and engorged on cut section. Microscopy showed a lower nephron nephrosis, i.e., the glomerular tuft was within normal limits; the capsular space was dilated and contained abundant albuminous debris; and the tubules showed necrosis and desquamation of the epithelium in the lower segment.

A majority of the tubules contained freshly extravasated blood and rather large heme pigment casts. The tubules contained spheruloradiate crystals, which were refractile under polarized light and which resembled sulfonamide crystals.

Comment. This patient presented a typical syndrome of severe renal injury due to incompatible blood. No recovery of renal function was observed in the ten days she survived. Time was lost in an ineffective effort to accomplish dialysis by peritoneal filling and emptying *via* needle punctures. The absorption of a large quantity of fluid which could not be recovered by aspiration from the peritoneal cavity produced pulmonary edema and clearly demonstrated the inadequacy and the danger of such a technique for dialysis. The sump drain functioned smoothly and with excellent efficiency until shock developed, probably because treatment of the urema was begun too late.

Case 13.—B.C. (BIH 93563): A 38-year-old bartender, entered a neighboring hospital for pneumonia and delirium tremens. Sulfadiazine (22 Gm.) and sodium bicarbonate (22 Gm.) were given in the first three days. He also received penicillin, paraldehyde, sodium phenobarbital, sodium bromide, demerol and hyoscine. Anuria occurred on the third day and sulfadiazine was omitted. No obstruction of the ureters was demonstrated.

After three days of anuria he was transferred to this hospital. He was cyanotic, orthopneic, disoriented and extremely irritable. His breath had a sweetish odor. There was limited expansion of the right side of the chest, with signs of consolidation in the right upper lobe and fine moist rales at both bases. The abdomen was distended. The skin showed a generalized maculopapular rash.

Temperature on admission was 100°F., pulse 100, respirations 30, blood pressure 150/100 mm. Hg. There was no urine. RBC was 3.43 million, Hg. 85%, and WBC 19,000. Blood NPN was 206 mg. per cent, BUN 170 mg. per cent and NaCl 464 mg. per cent. X-ray examination revealed haziness of the upper two thirds of the right lung and of the mid-lung field on the left and elevation of the right diaphragm. Abdominal films showed gaseous distention of the small intestine and ascites.

Penicillin and paraldehyde were given parenterally. Oxygen was given by mask and tube suction was instituted. Whiskey orally and sulfathalidine by tube were administered. The following day the patient received 500 cc. of blood, followed by 1,000 cc. of 10 per cent glucose in saline intravenously. A catheter recovered 100 cc. of grossly bloody urine, which was alkaline, with a specific gravity of 1018, and contained albumin and a sediment packed with erythrocytes. *E. coli*, enterococci, pyocyaneus and proteus were grown on culture of the urine. The rectal temperature ranged from 101° to 104° and the pulse rate from 100 to 120.

On the third hospital day the blood NPN was 228 mg. per cent, blood urea N 203 mg. per cent, CO_2 combining power 36 vol. per cent, NaCl 496 mg. per cent and sulfadiazine level 11.4 mg. per cent. The RBC had increased to 5.1 million, Hgb. to 100 per cent and WBC to 23,000. There were no signs of pulmonary or peripheral edema. Intermittent peritoneal lavage through a flexible sump drain was instituted: 500 cc. of the irrigating solution* was allowed to remain for 15 minutes and then removed. 500 cc. of 10 per cent glucose in saline intravenously was given to balance the volume of aspirated gastro-intestinal fluid. The urine output for that day totalled 10 cc. Thereafter, the total fluid intake exceeded the volume withdrawn from the gastro-intestinal tract by 1,000 cc. per day.

*Composition and preparation of irrigating solution as in previous case.

On the following day the patient appeared less euphoric, more rational and not quite as dyspneic. By evening minimal edema of the legs was apparent. The blood NPN had fallen to 186 mg. per cent and the CO_2 combining power to 26 vols. per cent. The blood calcium was 5.2 mg. per cent and the blood phosphate 12.0 mg. per cent. The serum protein level was 5.27 Gm. per cent (3.16 Gm. of albumin and 2.11 Gm. of globulin). Sodium lactate (10 cc. of molar solution) and calcium gluconate (80 cc. of 10 per cent solution) were given intravenously and sodium lactate and sodium bicarbonate solution were given hourly *via* the Miller-Abbott tube. The urine output was 45 cc. Urine culture was sterile.

The next (fifth) day, temperature, pulse and respiratory rate rose sharply. The blood NPN and BUN were 170 and 147 mg. per cent respectively and the NaCl was 574 mg. per cent. The CO_2 combining power had dropped to 22.5 vols. per cent. Only 15 cc. of urine were obtained from the bladder. The patient expired that evening, after 8 days of anuria.

Peritoneal lavage lasted a total of 50½ hours. During that time only 37 Gm. of urea was recovered (the urea clearance varied from 1.7 to 5.6 cc. per minute). Approximate measurement indicated that of the total inflow of 52.75 liters of irrigating solution, 49.25 liters were recovered, leaving a deficit of 3.5 liters, which was retained by or absorbed from the peritoneal cavity.

Postmortem examination revealed approximately 2,000 cc. of turbid yellow fluid in the pelvis. Smear of this fluid demonstrated *E. coli*. There was a fine, flaky fibrin deposition in the pelvis and slight injection of the pelvic peritoneum extending into the lateral gutters. There was consolidation of the entire upper lobe of the right lung and patchy consolidation of the upper lobe on the left. The remaining lobes of the lungs showed moderate edema. The kidneys weighed 290 Gm. each. Microscopically they showed a lower nephron nephrosis, i.e., the glomeruli were normal, but there was necrosis, desquamation and dislocation of the tubular epithelium of the lower portion of the nephron. In addition the proximal convoluted segment showed an extreme degree of cloudy swelling and droplet degeneration. A few tubules contained reddish brown amorphous casts and were surrounded by an interstitial exudate of lymphocytes, plasma cells and eosinophiles. These findings were most marked in the corticomedullary juncture.

Comment. The renal damage was apparently the result of suldiazine intoxication. No recovery of renal function was observed in the eight days the patient survived after the onset of anuria. The irrigation was inefficient for reasons that are obscure. Moreover, the infection of the peritoneal cavity was inexplicable rapid.

Case 14.—E.A. (BIH 94529): A 24-year-old white female was transferred in a moribund state from another hospital, where she had been treated for 40 days for progressive uremia resulting from subacute glomerulonephritis. Her daily urine output was 400-700 cc. the first week, less than 100 cc. the third week, less than 60 cc. the fourth week. The blood urea nitrogen had risen to 112 mg. per cent. The clinical course was progressively downhill, with hematemesis, occasional convulsions and eventually pulmonary edema, in spite of restricted fluid administration. It was felt that though the prognosis was grave, improvement by peritoneal irrigation might facilitate some recovery of renal function.

On admission to the Beth Israel Hospital, the patient had pulmonary edema, subcutaneous edema and ascites. The blood NPN was 308 mgm. per cent, blood urea N 236 mg. per cent, CO_2 combining capacity 21.5 vols. per cent, Hgb. 20 per cent, hemato-

crit 10 per cent, RBC 1.08. Intermittent irrigation* was carried out for 21 hours. The total inflow was 17.5 liters, total outflow 17.5 liters, total urea removed 39 Gm., average blood urea clearance 8.5 cc. per minute. Thereafter the patient died. The peritoneal outflow fluid remained sterile.

Postmortem examination revealed anasarca, severe pulmonary edema and congestion, early bronchopneumonia and multiple small areas of hemorrhage in the gastric mucosa. Several fine deposits of fibrin were found in the pelvis, without evidence of inflammation or suppuration. The kidneys showed advanced subacute glomerulonephritis.

Comment. At this stage in our clinical experience we had concluded that to avoid absorption of irrigating fluid it should contain not less than 1% gelatin and 1% glucose. We could not determine how effective such concentrations would be for the abstraction of edema fluid. We decided to avoid gross modifications of this formula in the future except perhaps in a case such as this one, in which the edema is so threatening as to compel the emergency use of a much more hypertonic solution. This patient was near death on admission. Fluid absorption was avoided, but not enough time was available to test the ability of this formula or a similar one with greater hypertonicity to remove the retained fluid. It was clear also that in addition to the composition of the fluid, the avoidance of a stagnant pool in the cul-de-sac was essential to prevent absorption. While we were confident that we could now handle fluid and electrolyte balance effectively, the problem of the prevention and control of peritonitis still remained.

Case 15.—E.H. (BIH 94733): A 22-year-old man underwent partial lobectomy for bronchiectasis at another hospital. The operative procedure lasted over five hours and was followed by several hours of shock. During and immediately after operation 2000 cc. of blood were given. On the third postoperative day, because of anemia, 500 cc. of blood was given. There was no clinical evidence of transfusion reaction and no sulfonamide drug was given.

Oliguria was noted throughout the postoperative period. The total urine volume per 24 hours in the first postoperative day was 450 cc., in the second day 450 cc., in the third 280 cc. and in the fourth 136 cc. On the fourth postoperative day the blood NPN was found to be 120 mg. per cent and the patient complained of severe bilateral costovertebral angle pain.

He was transferred to this hospital. Peritoneal irrigation* was begun the afternoon of the fifth postoperative day and was continued without interruption for 48 hours. The outflow fluid remained sterile. A substantial removal of nitrogenous material and reduction in blood NPN was accomplished (see Fig. 13 and Table VI). Urine output increased so that peritoneal irrigation was discontinued in anticipation of renal recovery. Rapid improvement in renal function occurred.

The patient was discharged in excellent condition on the twenty-first postoperative day, at which time the blood chemistry was normal, the urine was free of albumin or cells, but was alkaline and of low specific gravity. The renal urea clearance was still

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*Composition and preparation of solution as in previous two cases except for an increase in glucose concentration to 1 per cent. Technique of irrigation as in Cases 12 and 13.

*Composition of solution and conduct of irrigation as in the previous case.

only 40 cc/min. Two months later, the blood and urine were normal but urea clearance (47 cc/min) was still below normal.

Comment. The renal injury was probably due to surgical shock, although the flank pain suggests some other agent. Peritoneal irrigation was started on

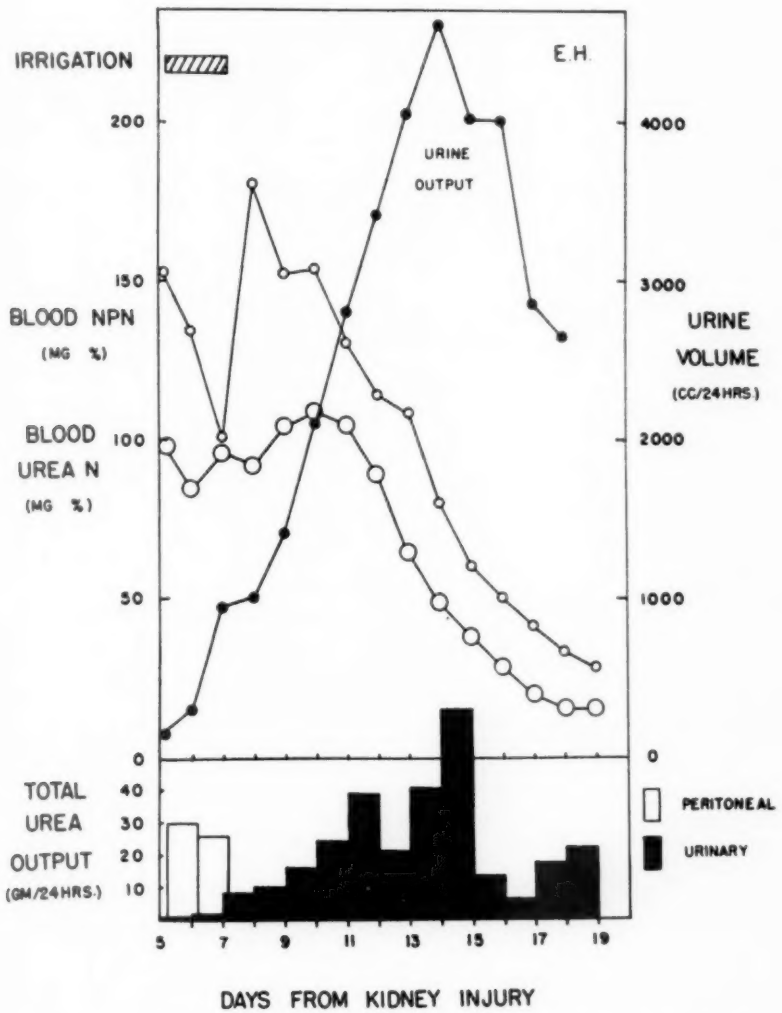

Fig. 13. Case 15.—(Cross-hatched bar indicates intermittent irrigation.)

the fifth day of oliguria and was discontinued on the seventh day, when the urine output reached 1000 cc. In spite of a linear increase in daily urine output, the blood NPN rose immediately after discontinuance of peritoneal irrigation. It was not until the 11th day, when the daily urine volume reached 3000 cc., that the urinary urea clearance value equalled the peritoneal urea clearance value. A significant decline in blood urea N then began. It is

TABLE VI—*Case 15*

Day (from kidney injury)	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th
Peritoneal fluid:															
Urea N (mg. %)	..	44	52	..	..	..	..	..	..	..	..	..	..	..	..
Urea clearance (cc./min.)	..	11	10	..	..	..	..	..	..	..	..	..	..	..	..
Culture	..	sterile		..	..	..	..	..	..	..	..	..	..	..	..
Urine:															
Urea N (mg. %)	370	332	378	415	562	507	644	624	468	658	156	292	292	390	..
Urea clearance (cc./min.)	1.84*	2.04*	4.37*	5.08*	7.7*	7.98*	11.6*	15.3	17.4	37.8	10.0	24.3	23.2*	41.0*	..
Specific gravity	1.001	1.005	1.006	1.005	1.003	..	1.002	1.008	1.004	..	..	..	1.010	1.012	1.002
Reaction	alk.	acid	acid	alk.	acid	..	alk.	alk.	alk.	..	..	..	acid	alk.	alk.
Albumin	4+	3+	3+	3+	2+	..	2+	1+	2+	..	..	..	1+	0	0
Cells	WBC	WBC	WBC	WBC	WBC	..	WBC	WBC	0	..	..	..	0	0	0
	RBC	RBC	RBC	RBC	RBC	..	..	..	0	..	..	..	0	0	0
Culture	*B. pyocyaneus*		..	..	..	..	..	..	..	..	..	..	..	..	..
Blood:															
CO_2 cap. (vol %)	36	32	29	..	57	..	..	..	53	..	..	..	..	..	..
Cl^- (as NaCl mg. %)	414	520	558	..	480	..	486	..	..	..	..	..	..	..	..
PO_4^{--} (mg. %)	9.5	..	..	..	..	7.2	..	..	5.1	..	..	..	..	..	4.7
Ca^{++} (mg. %)	10	..	10.8	..	10.5	10.2	..	..	10.8	..	..	..	..	..	11.3
Plasma protein (Gm. %)	5.7	..	5.8	..	..	5.4	6.2	..	..	..	..	..	..	..	..
Hemoglobin (Gm. %)	12.6	..	..	..	11.6	..	..	..	10.8	..	..	..	11.3	..	..
Arterial Blood Pressure (mm. Hg)	150/80	150/80	170/70	160/70	160/70	..	160/70	145/75	155/80	180/110	..	150/110	..	..	..
Fluid exchange:															
Peritoneal inflow (L.)	..	28.6	23.4	..	..	..	..	..	..	..	..	..	..	..	..
Peritoneal outflow (L.)	..	29.2	23.7	..	..	..	..	..	..	..	..	..	..	..	..
Lactate M (cc.)	..	..	120	240	320	160	..	..	..	..	..	..	..	..	..

*Renal urea clearance at urine flow rates of 2 cc/min. and higher, and urea clearance by peritoneal irrigation have been calculated by the formula [15,16] for "maximal urea clearance", *i.e.* maximal clearance (cc./min.) $= \frac{UV}{B}$, where U is the concentration of urea (mg. %) in the urine or peritoneal outflow fluid, V is the flow rate (cc./min.) of urine or peritoneal irrigating fluid, and B is the average concentration (mg. %) of urea in the blood during the period of collection of urine or peritoneal fluid. The average normal "maximal clearance" value for a human adult is 75 cc./minute.

At urine flow rates below 2 cc/min. the "standard urea clearance" was calculated according to the formula [15,16]: standard clearance (cc/min.) $= \frac{U\sqrt{V}}{B}$. The average normal "standard clearance" is 54 cc./minute.

Urinary urea clearance values marked with an asterisk are those which have been calculated as "standard clearances" and multiplied by 75/50 to facilitate comparison with the remaining "maximal clearances" in terms of the fraction of the average normal urea clearance attained.

likely that recovery in this instance would have occurred without peritoneal irrigation.

Case 16.—J.P.M. (BIH 94966): A 22-year-old woman, received 2500 cc. of plasma and 500-1000 cc. of Type B blood for post partum hemorrhage and shock. Another transfusion of 100 cc. of Type B blood given 8 days later for anemia caused generalized pain, headache and violent vomiting. Investigation disclosed that the patient's blood type was O.

The patient voided 730 cc. of bloody urine in the first day following the transfusion reaction, and but 80 cc. of bloody urine the next day. Intravenous fluid therapy included 200 cc. of 12½ per cent glucose, 500 cc. of Hartman's solution and 1000 cc.

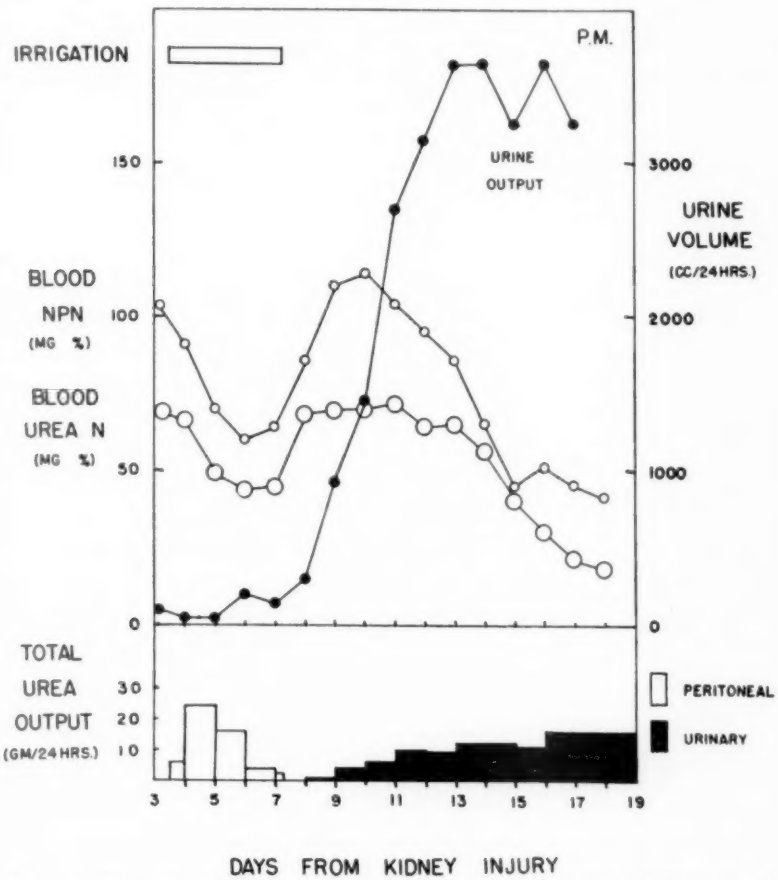

Fig. 14. Case 16.—(Open bar indicates continuous peritoneal irrigation.)

of 5 per cent glucose in water. Hot packs were applied to the costovertebral angles. On the third day following the transfusion reaction the patient voided 30 cc. of dark urine, her blood NPN was found to be 78 mg. per cent. She was then transferred to us.

Upon admission the patient was extremely pale and mildly edematous. Blood findings included RBC 2.6 million, Hgb. 50%, WBC 15,000, NPN 103 mg. per cent, CO_2 combining power 40 vols. per cent, NaCl 502 mg. per cent, phosphate 9.0 mg. per cent, calcium 9.7 mg. per cent. A catheterized urine specimen disclosed: sp. gr. 1003, acid reaction, albumin 4+, WBC 8-10 hpf, RBC 10-12 hpf.

TABLE VII—*Case 16*

Day (from kidney injury)	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th
Peritoneal fluid:																
Urea N (mg. %)	24	31	19	6.1	..	..	..	..	..	..	..	..	..	..	..	..
Urea clearance (cc./min.)	11.1	13.9	9.5	3.1	..	..	..	..	..	..	..	..	..	..	..	..
Culture	..	sterile	..	..	*E. coli*	..	..	..	..	..	..	..	..	..	..	..
Urine:																
Urea N (mg. %)	68.6	29.3	19.5	39.5	156	205	209	201	201	146	160	161	161	215	240	..
Urea clearance (cc./min.)	..	..	..	..	1.21*	1.82*	3.23*	3.76*	5.14*	5.05	6.48	8.13	10.1	20	25.5	25.7*
Specific gravity	1.003	1.011	..	1.001	1.008	1.008	1.004	1.007	..	1.008	1.002	1.003	1.004	1.004	..	..
Reaction	acid	acid	alk.	alk.	alk.	alk.	alk.	alk.	..	alk.	alk.	alk.	alk.	alk.	..	..
Albumin	4+	4+	4+	4+	4+	4+	3+	2+	..	2+	3+	2+	2+	2+	..	..
Culture	*E. coli*	*E. coli*	*E. coli*	*E. coli*	*E. coli*	..	sterile	..	sterile	..	..	..	..	..	..	..
Blood:																
CO_2 cap. (vol. %)	40	29	34	35	46	..	59	60	..	..	..	..	..	..	..	..
Cl^- (as NaCl mg. %)	502	..	604	..	..	..	..	..	..	..	..	..	..	..	..	..
PO_4^{--} (mg. %)	9	..	..	..	..	..	..	6.7	..	..	..	7.1	..	..	3.6	..
Ca^{++} (mg. %)	..			..	..	..	..	6.3	..	..	..	8.0	..	..	9.1	..
Plasma protein (Gm. %)	5.34	..	..	5.27	..	..	..	..	..	5.07	..	..	..	5.99	..	..
Hemoglobin (Gm. %)	..	9.6	8.7	8.0	..	..	7.3	..	..	10.0	..	11.4	..	10.5	..	..
Arterial Blood Pressure (mg. Hg)	110/60	110/60	120/60	120/70	130/70	120/50	110/70	110/80	140/80	110/60	104/64	..	..	..	..	130/80
Fluid balance:																
Peritoneal inflow (L.)	17.6	34.6	35.6	35.5	10.3	..	..	..	..	..	..	..	..	..	..	..
Peritoneal outflow (L.)	17.8	34.8	36.0	35.5	11.0	..	..	..	..	..	..	..	..	..	..	..
Lactate M (cc.)	..	160	320	320	160	160	80	80	..	..	..	..	..	..	..	..
Blood (cc.)	..	..	..	500	..	..	..	500	..	..	..	..	..	..	..	..

*See footnote to Table 6.

Peritoneal irrigation was carried out by a technic of continuous flow at a rate of 21-31 cc/min. from a small rubber inflow catheter in the right upper quadrant to the sump drain in the pelvic cul-de-sac. The solution was that used in the last case. Irrigation was carried out without difficulty for 89 hours. The effect upon the blood NPN and urea is shown in Figure 14 and Table 7. A total of 52.5 Gm. of urea was removed and a urea clearance value of 13.9 cc/min. was attained. The patient's clinical appearance did not change greatly.

Auxiliary treatment during this period included: penicillin (50,000 units every three hours), water soluble vitamins given intramuscularly, 5 per cent glucose in water given intravenously (1-2 liters per day) containing 160-320 cc. of molar sodium lactate solution, two 500 cc. transfusions of type O blood, and gastrointestinal suction drainage *via* a Miller-Abbott tube.

On the last day of irrigation a few *E. coli* were found in one sample of outflow fluid. A subsequent sample gave no growth, but a smear showed scattered polymorphonuclear leucocytes containing a few phagocytosed gram negative bacilli. Streptomycin was given (0.5 Gm. intramuscularly every three hours) for one and one-half days (total 9.5 Gm.) and penicillin administration (total dosage 3.9 million units) was continued for two and one-half days thereafter. No clinical evidence of peritonitis appeared.

Two days after cessation of irrigation the blood NPN and urea N concentration rose to higher levels than those found on admission. But diuresis had started by this time so that peritoneal irrigation was not resumed. Steady improvement in renal function occurred. When the patient was discharged well twenty days after the transfusion reaction, the daily urine output was 3500 cc, with a urea content of 16 Gm. (renal urea clearance 25 cc/min), sp. gr. 1004 and 2+ albumin.

Six weeks later the patient was well. The urine was free of ablumin and showed a sp. gr. of 1007. The blood urea clearance was 48 cc/mm. Blood chemistry was normal.

Comment. Continuous peritoneal irrigation carried out for 89 hours produced a substantial reduction in azotemia, although increasing acidosis required sodium lactate therapy. *E. coli* was grown from the peritoneal outflow fluid on one occasion on the last day of irrigation. Clinical peritonitis was not in evidence. Renal recovery first became manifest on the ninth day after the transfusion reaction and progressed so as to restore normal blood chemistry within the next six days. Significant impairment of renal function was still manifest six weeks thereafter.

It cannot be said that recovery would not have taken place without peritoneal irrigation. Spontaneous diuresis may occur in patients suffering from a transfusion reaction about the time this patient showed it, or a few days later.

Case 17.—A.M. (BIH 95349): A 46-year-old man with uremia, malignant hypertension, left hydronephrosis, congestive heart failure and anemia seemed moribund after eight days of hospital care. Peritoneal irrigation was requested by the attending physicians, who considered it remotely possible that the unilateral hydronephrosis was contributing to the hypertension, and that nephrectomy might be undertaken if the uremia could be corrected.

With this slim hope in mind, *continuous irrigation by an inflow catheter and sump drain at a flow rate of 25 cc/min. was started.* At that time pulmonary edema was present. The blood NPN was 186 mg. per cent, BUN 138 mg. per cent, CO_2

combining power 22 vols. per cent, NaCl 332 mg. per cent, Ca 7.7 mg. per cent, phosphate 16.0 mg. per cent. Urea clearance values of 16-18 cc/min. were attained. Sodium lactate (160 cc. of molar solution), given intravenously, failed to raise the CO_2 combining power. A smear of the outflow fluid taken the evening of the first day of irrigation showed a few gram negative rods which did not grow in culture. *E. coli* in pure culture was grown from the peritoneal outflow fluid after 24 hours. Furacin, known to be effective against gram negative organisms when applied topically, was added to the irrigating solution to a concentration of 1/40,000.* The peritoneal outflow fluid yielded no growth one hour after the Furacin was added to the irrigating solution, but a culture taken five hours later showed a small growth of *E. coli*.

The patient's general condition remained very poor and he expired after 36 hours of peritoneal irrigation.

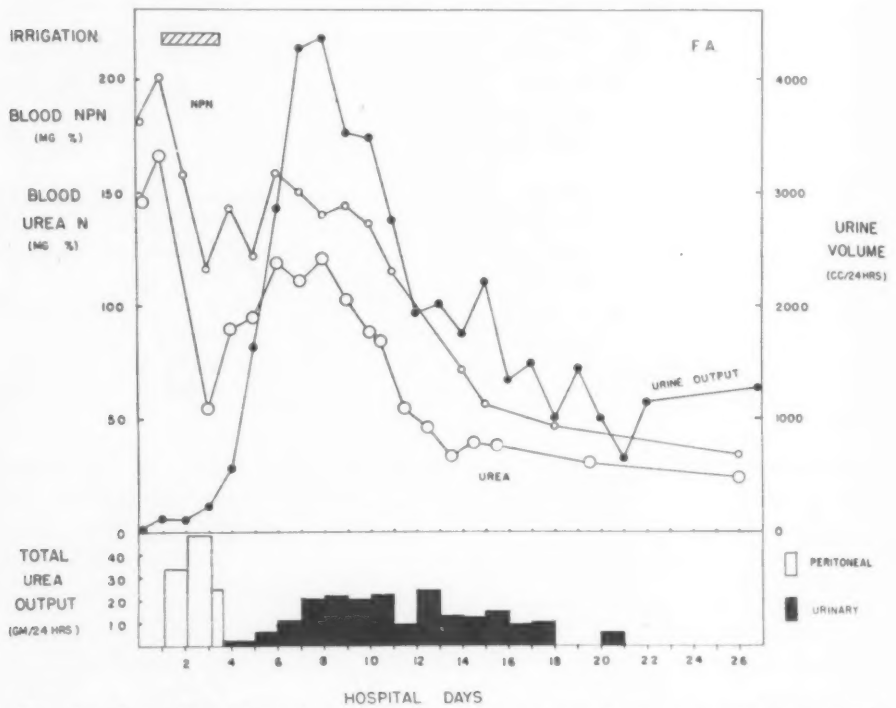

Fig. 15. Case 18.—(Cross-hatched bar indicates intermittent peritoneal irrigation.)

The amount of protein removed** by the irrigation was 71.7 Gm. in 36 hours.

Postmortem examination disclosed no evidence of peritonitis. There was enlargement of the heart and pulmonary edema and congestion. There was a stricture at the left uretero-vesical junction with marked dilatation of the left ureter and kidney pelvis, both of which contained purulent fluid. The histologic examination of the kidneys disclosed necrotizing arteriolitis, arteriolosclerosis and arteriosclerosis.

*Furacin in this concentration was found to be effective against E. coli *in vitro* and to a lesser extension *in vivo* (17). Experiments on dogs suggested that the toxic effects of absorption of Furacin would be avoided at this concentration.

**The method of analysis for the protein was as follows: 50 cc. samples were brought to a pH of 4.8-4.9 by the addition of 100 cc. of an acetate buffer solution, boiled for thirty minutes and then filtered. The precipitates were washed, dried and weighed. No protein is recovered as a precipitate from the irrigating fluid itself.

TABLE VIII—*Case 18*

Hospital day	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	14th	17th	20th
Peritoneal fluid:													
Urea N (mg. %)	87	60–67	59–52	..	..	..	..	..	..	..	..	..	..
Urea clearance (cc./min.)	10	14–20	19–13	..	..	..	..	..	..	..	..	..	..
Culture	*B. subtilis*		..	..	..	..	..	..	..	..	..	..	..
Urine:													
Urea N (mg. %)	133	149	158	168	188	187	231	255	274	299	326	294	287
Urea clearance (cc./min.)	..	..	1.2*	1.5*	2.6*	3.1*	5.9	6.3	6.0	7.5	12.5*	10.9*	10.9*
Specific gravity	..	..	1.008	1.005	1.010	1.010	..	1.010	1.008	1.018	1.005	1.007	1.013
Reaction	..	..	alk.	alk.	alk.	alk.	..	alk.	alk.	alk.	alk.	alk.	acid
Albumin	..	..	4+	3+	2+	2+	..	1+	1+	2+	1+	0	0
Culture	*E. coli*	..	..	..	..	..	..	..	..	*aerogenes* *E. coli*	..	..	..
Blood:													
CO_2 cap. (vol. %)	28	28	25	35	35	33	38	39	..	..	38	..	..
Cl^- (as NaCl mg. %)	480	..	606	592	440	..	..	548	..	..	..	..	..
PO_4^{--} (mg. %)	11.1	..	..	..	8.3	..	3.6	..	..	7.0	4.0	..	3.9
Ca^{++} (mg. %)	4.8	..	10.5	..	10.5	..	8.9	..	..	8.2	8.3	..	10.1
Plasma protein (Gm. %)	6.7	..	6.9	..	..	5.6	..	..	..	..	..	..	..
Hemoglobin (Gm. %)	..	..	12.5	10.1	..	8.7	10.1	..	..	10.4	10.0	..	..
Arterial Blood Pressure (mg. Hg)	175/85	200/100	195/90	190/100	175/90	170/90	170/100	155/80	..	155/95	120/70	130/70	..
Fluid exchange:													
Peritoneal inflow (L.)	15.3	35.6	24.5	..	..	..	..	..	..	..	..	..	..
Peritoneal outflow (L.)	15.0	33.9	24.3	..	..	..	..	..	..	..	..	..	..
Lactate M (cc.)	160	240	160	..	..	..	..	..	..	..	..	..	..
Blood (cc.)	500	500	..	..	..	..	..	..	..	..	..	..	..

*See footnote to Table 6.

Comment. This patient was moribund when irrigation was started. Nitrogen removal proceeded efficiently, but survival was not long enough to effect a significant change in the uremic state. *E. coli* appeared in the peritoneal outflow fluid within 12-24 hours.

Case 18.—F.A. (BIH 97808): A 39-year-old female was transferred to the Beth Israel Hospital because of post-eclamptic oliguria and uremia six days after Caesarean section. Pre-eclampsia during pregnancy three years earlier had been terminated by Caesarean section because of a deformed pelvis. On admission there was pitting edema, the arterial pressure was 150/90 mm. Hg., the fundi were normal, the blood NPN was 186 mg. per cent and the CO_2 combining power 20 vols. per cent.

The patient was observed for about 20 hours, during which her condition deteriorated considerably. She became drowsy and apathetic and exhibited hypocalcemic twitchings and tetany. The bladder contained 25 cc. of turbid, alkaline urine with a sp. gr. of 1003, albumin (4+), red and white cells, E. coli, gram-positive cocci and diphtheroids. At this time the blood NPN was 202 mg. per cent, the serum calcium 4.8 and the serum phosphate 11.1 mg.

The intestine was intubated. *Intermittent peritoneal irrigation was carried out with 500 cc. volumes of solution (1% gelatin and 1% glucose) which were removed after a ten-minute period.* The patient seemed moribund during the first 12 hours, but thereafter clinical improvement concomitant with improvement in blood chemistry occurred (Table 8 and Figure 15). The intravenous fluid was limited to 1000-1500 cc. per day, which included whole blood, 15 per cent glucose in water, molar sodium lactate solution (160-240 cc.) and 10 per cent calcium gluconate (30 cc. or more). Penicillin and the water soluble vitamins were given intramuscularly. Irrigation was terminated after 60 hours. The sump was removed. *B. subtilis* was found in the outflow fluid throughout the irrigation period. There were equivocal signs of peritoneal infection, which disappeared when the irrigation was stopped.

Diuresis began within a day after the cessation of irrigation (10 days after renal shutdown). In spite of rapidly increasing urine volumes the recovery of concentrating power was slow, so that a secondary rise in blood nitrogenous levels occurred. During the next four weeks she regained mental clarity, a normal arterial pressure and clinical well-being. Nausea and vomiting were the last symptoms to disappear. On discharge the blood chemistry was normal, the urine was acid, free of albumin or sediment with a sp. gr. as high as 1.018. Renal blood urea clearance, however, was less than 1/7 of normal.

Comment. Little is known of this patient's renal function prior to the eclamptic convulsions. The slow renal recovery after the onset of diuresis and the markedly reduced function at the time of discharge suggest reduced renal function prior to the second pregnancy. The patient was so sick when irrigation was started that it is doubtful if she would have survived long enough to permit spontaneous renal recovery. For this reason we believe that the irrigation therapy was responsible for the induction of diuresis. *B. subtilis* is considered non-pathogenic. It was the sole organism recovered from the peritoneal outflow fluid. Its pathogenicity in this case was not determined.

DISCUSSION

Of the group of 18 patients, in this and a previous report, 4 recovered and 14 died (Table IX). Of the 14 patients who died, 5 had renal lesions which can be assumed to have been irreversible, 8 had lower nephron injuries and

TABLE IX—

Case	B. I. H. #	Age yrs.	Cause of Renal Injury	Duration of Oliguria (days from onset to death or recovery)	Onset of Diuresis (days after renal injury)	Adequate Renal Function Recovered (days after renal injury)	Initiation of Irri (days after or (d renal injury) fore
1*	82347	49	Carcinomatous obstruction of ureters	..	..	..	..
2*	83789	14	Incompatible blood transfusion	13	13	16	3½
3*	85197	51	Sulfathiazole intoxication	15	15	18	10
4*	..	19	Incompatible blood transfusion	8	..	..	2
5	88032	42	Carbon tetrachloride intoxication	12	..	..	10
6	88238	55	Subacute bacterial endocarditis ? acute glomerulonephritis	? weeks	..	..	..
7	88742	56	Post-operative peritonitis	13	9	..	4
8	91435	44	Unknown (chronic alcoholic)	29±	..	..	22±
9	91590	58	Intravenous infusion reaction	11½	..	..	10
10	91718	43	Unknown	30±	..	..	23±
11	92825	32	Sulfadiazine intoxication	17	12(?)	..	7
12†	93042	36	Incompatible blood transfusion	10	..	..	8
13†	93563	38	Sulfadiazine intoxication	8	..	..	6
14†	94529	24	Subacute glomerulonephritis	40±	..	..	..
15†	94733	22	Surgical shock	7	7	11	5
16	94966	22	Incompatible blood transfusion	9	9	15	8
17	95349	46	Malignant nephrosclerosis	?	..	..	..
18†	97808	39	Eclampsia	10	10	16	7

*See reference 1.

†Irrigation by intermittent (filling and emptying) technic.

(Note: Flexible sump drain used in case 12 and thereafter.
Irrigation by continuous technic except as noted above.)

TABLE IX—*Summary of Clinical Data*

dequate Renal unction ecovered ys after al injury)	Initiation of Irrigation (days after or renal injury)	(days before death)	Duration of Irrigation (days)	Survival	Cause of Death
..	..	..	..	0	Cessation of treatment
16	3½	..	12½	0	Pulmonary emboli
18	10	..	7	+	
..	2	..	6	0	Pulmonary and cerebral edema; a
..	10	..	2	0	Pulmonary edema; confluent bron
..	..	10	10	0	Peritonitis
..	4	..	7½	0	Peritonitis; confluent bronchopne
..	22±	..	7	0	Peritonitis
..	10	..	1½	0	Uremia
..	23±	..	2½	0	Uremia; peritonitis
..	7	..	6	0	Uremia; peritonitis; cerebral e congestion and edema
..	8	..	2	0	Uremia
..	6	..	2	0	Pneumonia; uremia; peritonitis
..	..	1	1	0	Uremia; pulmonary edema
11	5	..	2	+	
15	3	..	4	+	
..	..	1½	1½	0	Uremia; pulmonary edema; infect
16	7	..	2½	+	

ıse of Death	Autopsy Data
t	
	Rheumatic heart disease; subacute bacterial endocarditis; early peritonitis
ral edema; shock	(No peritonitis)
nfluent bronchopneumonia	Lower nephron nephrosis; hepatitis
	Mitral stenosis and insufficiency; subacute bacterial endocarditis; chronic glomerulonephritis with acute exacerbation
bronchopneumonia	Peri-pancreatic necrosis and sepsis; biliary obstruction lower nephron nephrosis—mild, healing
	Tubular nephritis
	Lower nephron nephrosis
	Chronic and acute glomerulonephritis
cerebral edema; pulmonary	Lower nephron nephrosis
	Lower nephron nephrosis; cerebral and pulmonary edema
peritonitis	Lower nephron nephrosis
edema	Subacute glomerulonephritis
edema; infected hydronephrosis	Malignant nephrosclerosis; ureteral stricture

1 had tubular nephritis. Death could be attributed to uremia or pulmonary and cerebral edema in 5 of these cases, to peritonitis which resulted from irrigation in 3, to postpancreatectomy peritonitis in 1, in lesser degree to peritonitis in 3, to pulmonary embolus in 1 who had recovered renal function, and to terminal carcinoma in 1.

The cause of renal failure in the 4 who survived was sulfathiazole sensitivity, surgical shock, incompatible blood, and eclampsia. In the case of surgical shock, the return of renal function would almost certainly have ensued without peritoneal irrigation.

TABLE X*—*The Occurrence of Peritoneal Infection During Irrigation*

Case	Organisms	Appearance of positive cultures (day of irrigation)	Total duration of irrigation (days)
1	0	..	two 2 day periods
2	*E. coli*	12	12 (discontinuous)
3	*E. coli*	3	7
4	*E. coli, staph. albus, Cl. welchii, enterococci*	6	6
5	0	..	2
6	*E. coli*, gram positive diplococci,	7	10
	B. pyocyaneus, B. subtilis	10	
7	(streptococci and diphtheroids)	(before irrigation)	
	E. coli	3	7½
8	*E. coli, B. aerogenes*, Friedlander's bacillus	7	7
9	0	..	1½
10	*Staph. albus* and diphtheroids	2½	
	E. coli	2 days later	2½
	E. coli	4 days later	
11	*E. coli*	4½	6
12†	0	..	2 (44 hours)
13†	*E. coli*	2	2 (50 hours)
14†	0	..	1 (21 hours)
15†	0	..	2 (45 hours)
16	*E. coli*	4	4
17	*E. coli*	1	1½
18†	*B. subtilis*	1	2½

*We are indebted to Dr. Fritz Schweinburg of the Department of Surgical Research for bacteriologic studies.
†Irrigation by intermittent (filling and emptying) technic.
(Note: Flexible sump drain used in case 12 and thereafter. Irrigation by continuous technic except as noted above).

These mortality data, however, are of no great significance. These patients, who could be expected to die, were, we believe, justifiably utilized as experimental subjects for the purpose of perfecting a hopeful therapeutic technic which was and still is in an evolutionary stage.

Peritonitis (Table X): It is obvious that this method is not a clinically acceptable one unless and until it can be utilized with reasonable assurance that peritonitis will not occur or will be curable if it does occur. In only 6 of the 18 patients reported in this and in the previous paper, did the peritoneal outflow fluid remain sterile throughout the period of irrigation and none of these six patients was irrigated for longer than 48 hours at a time. In two of the other 12 patients organisms were found in the outflow fluid

after 24 hours, in four after 72 hours, in five between 4-7 days and in one (Case 2) after twelve days of discontinuous irrigation. *E. coli* was found in 11 of the 12 patients, in eight in pure culture and in the remainder with *B. pyocyaneus,* gram-positive diplococci or *B. aerogenes.* In one case mixed organisms, including anaerobes, were recovered just before death, but the peritoneum was entirely free of reaction. In one patient with a prior postoperative streptococcal peritonitis, *E. coli* was grown in pure culture after three days of irrigation.

In half of the 12 patients with positive cultures from the outflow fluid, clinical and postmortem evidence of peritonitis was either lacking or equivocal. In the other half the intensification of antibiotic therapy when the positive cultures were obtained did not ameliorate the course of the peritonitis. But cessation of irrigation was followed by recovery from peritonitis and survival in two of these.

Since the sterility of the inflow fluid was not in doubt at any time, the other likely source of bacterial contamination was the sinus tract leading from the skin to the peritoneal sac. But organisms native to the skin and not susceptible to penicillin therapy (e.g., staph. albus, sarcinae, diphtheroids) were only rarely found in the peritoneal fluid. Since the special care given in the preliminary treatment of the skin, the protection of the abdominal wound and in the design and application of the sump drain and effective filtration of the air failed to prevent peritoneal infection with *E. coli,* it is conceivable that serosal irritation produced by peritoneal irrigation may have facilitated transmural migration of this organism from the intestinal canal.

In normal and nephrectomized rabbits and dogs following the intraperitoneal injection of a strong irritant *E. coli* was recovered in pure culture from the peritoneal cavity[18]. In a dog with *E. coli* peritonitis induced by an irritant, *E. coli* tagged with radioactive iodine was introduced into the gastrointestinal tract. Twenty-four hours later radioactivity to the extent of 0.1 per cent of that given was found in the washed peritoneal fluid sediment[19]. The irrigating solution used in patients failed to produce positive cultures in the peritoneum of normal dogs after ten days of filling and emptying the peritoneal cavity twice each day[18]. Dogs similarly treated after having been rendered uremic by bilateral nephrectomy, showed *E. coli* within six to nine days, except for those animals in which the *E. coli* of the intestinal canal had been eliminated by starvation plus intensive enteric administration of streptomycin and sulfaphthalidine[18].

The more rapid appearance of *E. coli* in uremic patients than in uremic animals may be due to the far greater resistance of dogs to this organism and to the more continuous exposure to the irritant in patients than was the case in the animal experiments.

Thus, it appears that migration *E. coli* through the bowel wall occurs more readily in the uremic state. This, both in man and animals, may be due

TABLE XI—*Urea Clearance by Peritoneal Irrigation:*
Flow rate and urea clearance during 24 hours of best performance in each patient. Comparison of continuous flow with filling and emptying technic.

CONTINUOUS					INTERMITTENT				
Case Number	Flow Rate (cc./min.)	Urea Clearance (cc./min.)	Averages Flow Rate	Averages Clearance	Case Number	Flow Rate* (cc./min.)	Urea Clearance (cc./min.)	Volume Introduced at Each Filling (cc)	Cycle† (min.)
2*	13	8			11	10–15	11	1000	45
2*	16	14	16	11.1	15	14	11	500	15
4	17	12.5			13	15	6	500	15
11	20	10			14	18	9	500	15
9	23	3			12	21	12	500	15
16	25	14							
5	25	22				Average 16	10		
10	26	19							
17	29	18.5			18	22.4	19.9	500	10
3*	29	21							
8	30	16							
7	33	22							
3	35	19							
6	37	34	39	23.8					
2	40	28.5							
1*	45	16							
1	60	23							
General average	31	18.5							

*Less than optimal flow rates included for comparison; not included in general average.

*Calculated from total volume introduced into the peritoneal sac each 12 or 24 hours.
†Equilibration period in each cycle, *i.e.*, time from end of introduction of fluid to start of withdrawal.

to a change in the physical state of the intestinal wall as well as to lowered resistance to contaminating organisms.

Since the evidence points to the intestine as the source of offending bacteria, an effective bactericidal agent for *E. coli* must be found. Streptomycin has been found to be of little or no therapeutic value, although its oral use for the preliminary reduction of intestinal bacteria has not been tested. The effectiveness of the newer antibiotics, i.e., polymyxin, bacillosporon B or duomycin will be examined in future cases.

Since the likelihood of infection increases with the duration of the irrigation period, the latter for the time being should be limited to 2-3 days. If contamination has already occurred, a rest period will in some instances allow the peritoneum to sterilize itself. Since such a rest period may be required, it is obviously desirable to utilize the method so as to obtain maximum dialyzing speed.

Efficiency of Peritoneal Irrigation: While the severity of the uremic state is not due to the azotemia, it varies roughly in parallel with the blood

Fluid Absorbed from Peritoneum During Irrigation:

TABLE XII—*Peritoneal fluid retained (deficit of outflow compared to inflow) during the 24 hours of irrigation which provided the best urea clearance.*

CONTINUOUS*				INTERMITTENT*				
Case	Non-electrolyte content of irrigating solution Glucose(%)	Gelatin(%)	Fluid retained (cc.)	Case	Cycle (min.)	Non-electrolyte content of irrigating solution Glucose(%)	Gelatin(%)	Fluid retained (cc.)
7	2	..	1000	12	15	0.5	1	700
8	2	..	4000	13	15	0.5	1	2000
11	1	0.5	4000	11	45	1	0.5	700
10	0.5	1	5900	14	15	1	1	0
17	1	1	100	15	15	1	1	—600
16	1	1	—200	18	10	1	1	600

*Flexible sump drain used in Case 12 and thereafter.

nitrogen level. To reduce the blood NPN by one-half in 48 hours, the blood urea clearance by peritoneal irrigation must be at least 20 cc/min. A clearance rate of 7-10 cc/min. may prevent a further rise in the blood NPN level or accomplish a very slow reduction, over a period of days. A few of our patients showed such a poor urea clearance, for which we cannot account.

It is not yet decided whether continuous or intermittent irrigation provides the more efficient dialysis. Table XI suggests that a flow rate of at least 25 cc/min. is required to produce maximal clearance by continuous irrigation. To obtain a corresponding value by the intermittent technic requires the use of shorter cycles than were used except in the last case. Analysis of Table XI indicates that, within the conditions tested, the efficiency of urea clearance is determined by the overall flow rate and not by the type of irrigation. High flow rates are readily accomplished by continuous irrigation without inconvenience to patient or attendants. A further

increase in overall flow rate by intermittent filling and emptying might be accomplished by further shortening the equilibration period or by an increase in the volume of fluid introduced at each filling. In many patients the latter is limited by the discomfort of abdominal distentions or by interference with breathing. Intermittent irrigation has the disadvantage of requiring the continuous attention of a trained attendant.

Table XII shows that the least fluid absorption occurred when 1% glucose and 1% gelatin were used to produce hypertonicity. In this respect continuous and intermittent irrigation were equally satisfactory with this solution. The composition of the fluid alone may not be wholly responsible for the avoidance of fluid absorption, since the flexible sump drain, which prevents puddling in the pelvis, was used with this fluid in all instances.

Edema. When oliguric patients are seriously overhydrated, not only is the intravenous therapy needed for the control of acidosis and starvation impeded but the problem of removal of excess fluid is created. Pulmonary and cerebral edema commonly cause the death of oliguric patients. A good deal of fluid may be removed by suction drainage of the intestine. If the edema is so severe that it is desirable to decrease it rapidly, increasing the hypertonicity of the dialyzing solution may be attempted. This must be done with caution. In Case 4 a solution of 5% gelatin and 2½% glucose withdrew fluid from the plasma so rapidly as to produce shock. Moreover, the hypertonicity may be responsible for the peritoneal irritation and by increasing it still further, infection may be even more likely. Excessive sodium administration and unreplaced protein loss contribute to generalized edema in the oliguric phase and delay diuresis. Anuria in tubular lesions may be due to obstruction to tubular flow from the inflammatory renal edema together with reabsorption of the entire glomerular filtrate rather than to decline in glomerular output[20]. If the kidney is rendered still more edematous by overhydration, diuresis is still further interfered with[21]. The omission of sodium chloride from the irrigating fluid rapidly abstracts it together with water from the extracellular fluid but such a rapid removal of body sodium so reduces the "available alkali"[22], the plasma volume[23], and the interstitial fluid volume as to be dangerous, apart from the simultaneous occurrence of intracellular overhydration[24]. Indeed, such salt loss may have been responsible for the failure of early clinical efforts in which peritoneal irrigation was carried out with simple glucose solutions (see reference 2).

Acidosis. Peritoneal irrigation with the solutions ordinarily used does not correct the progressive acidosis of uremia. While the total base in the solution is that of normal plasma, the chloride content is considerably higher and the bicarbonate considerably lower (see Fig. 9). Little of the total base, therefore, is available to neutralize the excess of acid radicles. Modification of the formula by the replacement of excess chloride by bicarbonate or lactate corrected the acidosis of two of three patients in whom it was tried, but the resulting alkalinity of the irrigating fluid may have contributed to

peritoneal irritation and infection. It is, therefore, considered inadvisable to to use the more alkaline solutions routinely. The acidosis is better-treated by providing as much carbohydrates as can be given so as to impede ketosis and reduce protein catabolism and by giving alkali intravenously. Uncorrected acidosis may impede the recovery of renal function[20].

Nutrition. The biochemical disorder in the uremic patient may be aggravated by the loss of protein into the irrigating fluid. The outflow fluid contains a heat coagulable protein, which has been measured in recent cases and found in concentrations varying from 20-220 mg. per cent. Still larger protein loss during peritoneal irrigation has been reported by others[7, 11, 25]. The total amount of protein lost in this way in our cases has been as much at 72 Gm. in 36 hours. Larger losses may occur when peritonitis sets in.

Since oral feeding is, as a rule, precluded because of ileus and since intravenous amino-acid feeding is severely limited because of the limited water allowance, whole blood and plasma are given for hemoglobin or plasma protein deficiency. The basal caloric requirement (1600 calories) cannot be met by intravenous feeding. Glucose in excess of 15% is undesirable because of its hypertonicity and the possibility of renal tubular damage[26, 27, 28, 29], although this may not be a serious factor if the infusion is given very slowly. One liter of 15% glucose provides only 600 calories. Absorption of glucose from the irrigating fluid varies with the concentration. The total absorption of glucose from a solution with a one per cent concentration has been found during continuous or intermittent irrigation to be only 4-5 Gm. per hour, or 96-120 Gm. per day, i.e., 360-480 additional calories. Hence starvation ketosis with acidosis is not completely prevented and usually requires alkali therapy.

Potassium and Magnesium. Although potassium is excreted in marked renal insufficienty so long as urine is secreted[30], so that potassium accumulation is rarely significant in chronic uremia[31, 32], potassium intoxication might become an important or even lethal factor in anuria[33]. Toxic levels of serum potassium in acute uremia have been reported[34, 35, 36, 37].

The excess potassium in uremia is probably eliminated by peritoneal irrigation. The irrigating solution contains potassium in a concentration equal to that in normal plasma (5 mEq/L) to prevent potassium depletion. Should Potassium intoxication occur potassium should be omitted from the solution and intravenous sodium and calcium therapy applied[37, 38]. Experimental[39, 40] and clinical[41] studies indicate that the administration of potassium (whether in the form of food, diuretic salts, or fragile transfused red cells) to severely oliguric patients should be avoided.

Similar considerations may apply to magnesium, but no increase in plasma magnesium was found in 13 recently reported instances of acute uremia[35]. Calcium is stated to be a specific antagonist of magnesium poisoning[42].

Calcium and Phosphate. An increase in serum phosphate and reduction in serum calcium, regularly reported in chronic[32] and acute[35] uremia, are

among the most striking of the chemical alterations observed in our patients. Calcium concentrations as low as 4.8 mg. per cent and phosphate as high as 11.1 mg. per cent are found. Tetany and convulsions are common, but these respond to intravenously administered calcium chloride or calcium gluconate. In certain acidotic patients, alkali therapy precipitates tetany, as would be expected because of the already low ionic calcium. Hyperphosphatemia is among the last of the chemical abnormalities to be corrected by peritoneal irrigation. In surviving patients a return to normal does not occur until some days after diuresis has set in. For these reasons, the phosphate salt has been omitted and the $CaCl_2$ concentration doubled in the irrigating solution. Even so there is need for intravenous calcium therapy. No systematic effort has been made to eliminate hypocalcemia by calcium feeding.

Adjuvant Therapy. Penicillin is given in large doses prophylactically. Streptomycin is given only if infection of the peritoneum or the urinary tract due to a susceptible organism occurs. It is not given prophylactically because of the rapid development of bacterial resistance. Sulfonamides are not given parenterally as a routine measure for fear that they might further damage the kidney, although this fear may not be warranted.

The water soluble vitamins are given parenterally in large doses in view of the likelihood that they are dialyzed out of the plasma by peritoneal irrigation, although there is no experimental evidence that this does happen. Only fresh blood is used for transfusion in order to avoid renal damage from a rapid breakdown of any considerable fraction of the infused cells.

An effort is made in all patients to pass the tip of a Miller-Abbott tube beyond the pylorus before starting peritoneal irrigation.

Renal Recovery. The pattern of renal recovery in our patients (and in those reported by others[43]) appears to consist first in a return of glomerular function followed by a slow improvement in tubular function. Following the onset of diuresis, there is usually a nearly geometric progression in the daily urine volume* to a maximum of 4 or 5 liters (3 cc/min), after which the volume declines. A urine volume as high as 9 liters per day (6 cc/min.) in this phase has been reported[45]. The urine has a specific gravity of 1.003 to 1.010, tends to be alkaline and has a urea concentration no greater than twice that of the plasma. Further evidence of inadequate renal function in this phase is the large loss of sodium chloride[45] which may produce rapid dehydration, if not anticipated and replaced. Thereafter, the urinary urea increases in concentration, and the blood urea clearance rises above 7.5 to 10 cc/min., with a concomitant fall in blood NPN. As the specific gravity rises signifying improved tubular function, the urine becomes acid, and the acidosis and hyperphosphatemia disappear. Complete tubular recovery was not observed in our surviving patients even after some months.

*These volumes remain well below the average normal glomerular filtration rate—120 cc/min and even well below the maximum urine flow of normal man—20 cc/min (44).

Selection of the Patient and Initiation of Irrigation: Patients in acute renal failure should not be considered suitable for dialysis therapy unless clinical evaluation indicates that the injury responsible for failure is reversible. This is often difficult to determine. Bichloride of mercury, carbon tetrachloride or other drug poisoning, toxic injury from acute infections, incompatible blood transfusion, traumatic shock, crush syndrome, acute nephritis, anuria complicating eclampsia, or acute renal damage superimposed on chronic renal disease which has been compatible with life, are examples of disorders that may be acceptable for dialysis. In many patients the renal failure is only one among several grave disorders, any of which may prove lethal even if renal recovery is possible.

Peritoneal irrigation does not heal the renal lesion. It simply reduces azotemia and improves electrolyte and fluid balance for a length of time which, it is hoped, will be sufficient to permit recovery of renal function.

Since the treatment to be applied should carry the smallest possible risk, there is much to be said for conservative treatment without resort to any special procedure. Many patients with acute renal lesions, if carefully managed, can recover even after two weeks of uremia[45]. Although occasional anuric patients have been observed to survive for as long as 3-4 weeks[46, 47], death usually supervenes within 10-14 days if recovery of renal function does not occur. There is widespread misunderstanding as to what the circumstances require. As a result patients in uremia are made worse and sometimes succumb to the burdens inflicted by unwise therapy. Overhydration is a common therapeutic abuse resulting in death from pulmonary or cerebral edema. On the other hand, dehydration will delay diuresis. Appropriate fluid and electrolyte therapy requires frequent reappraisal of the state of imbalance. What is lost by vomiting or diarrhea, by visible sweating and in the urine must be replaced. Not over 1000 cc. over and above this total is to be given daily, whether parenterally or orally. To this 1000 cc., 100-150 grams of dextrose and water soluble vitamins are added. Alkali and calcium are also added, as needed. Sodium chloride is not given except as it is lost in substantial amounts from the stomach. The small amount lost *via* the skin is not significant. Moderate hypochloremia *per se* produces no symptoms and requires no therapy, while excess salt may prove disastrous. An effort is made to maintain optimal conditions for urine production in terms of cardiac output, blood volume, arterial pressure, and hemoglobin concentration.

If oral alimentation is possible, it must respect the foregoing fluid and electrolyte requirements. A non-distending carbohydrate is desirable since the requirement for dextrose cannot be met by intravenous therapy. Protein may be given also, even though nitrogenous residues cannot be excreted, for it is extremely doubtful that the azotemia itself is seriously deleterious in uremia. By a regimen of this sort, survival can be anticipated in many types

of acute renal failure which are capable of reversing themselves within two to three weeks.

Other technics are also available. Trueta's studies[48] suggest that neurogenic diversion of renal cortical blood flow may account for some types of acute renal failure. Abolition of this reflex by prolonged or fractional spinal anesthesia, splanchnic block or renal denervation deserves more study.

At the present time, however, dialysis of the blood is the only direct approach with some promise of therapeutic benefit, but peritoneal dialysis cannot expect to become an acceptable method until an effective antibiotic against contaminating organisms is found. One can scarcely anticipate as rapid and complete a removal of retention products by peritoneal dialysis as by Kolff's dialyzer[49]. The clinical problem varies so widely from one case of renal failure to another that flexibility of adaptation is essential no matter which of the two methods is used. If the Kolff technic can be controlled in all 29 aspects and made sufficiently flexible to meet the requirements of each case it has obvious advantages and a wider margin of safety than peritoneal dialysis. Experience will eventually decide the possibilities and advantages of each method. The introduction of a long aspirating tube into the ileum combined with an irrigating fluid which contains sodium sulfate to withdraw retention products into the gut has recently been reported to give good urea clearances[50].

When in the course of the uremic state any one of these measures should be applied remains an open question. Advocates of conservative therapy would presumably welcome them only when a progressively rapid deterioration is in evidence. This may be too late for any therapy. If, as is so often the case, the patient comes under observation in an already far advanced state of renal failure, it will be difficult to defend the exclusive use of conservative measures if rapid dialyzing technics are at hand. The fact that diuresis frequently sets in soon after blood levels of NPN and urea nitrogen show a substantial fall suggests that the uremia itself may act as a block to recovery of renal cellular function. For this reason it may be desirable to institute such treatment early rather than late.

If further study affirms the validity of this concept, the prospect of accelerating return of renal function will be better than is now possible by good conservative therapy alone.

CONCLUSION

Data obtained in 14 additional patients in renal failure are presented and evaluated. The present method of performing peritoneal irrigation is described, and various aspects of the care of the patient in renal failure are discussed. The continuing hazard of peritonitis makes it necessary to regard the method as still in the experimental stages, and should not be considered for routine clinical use.

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